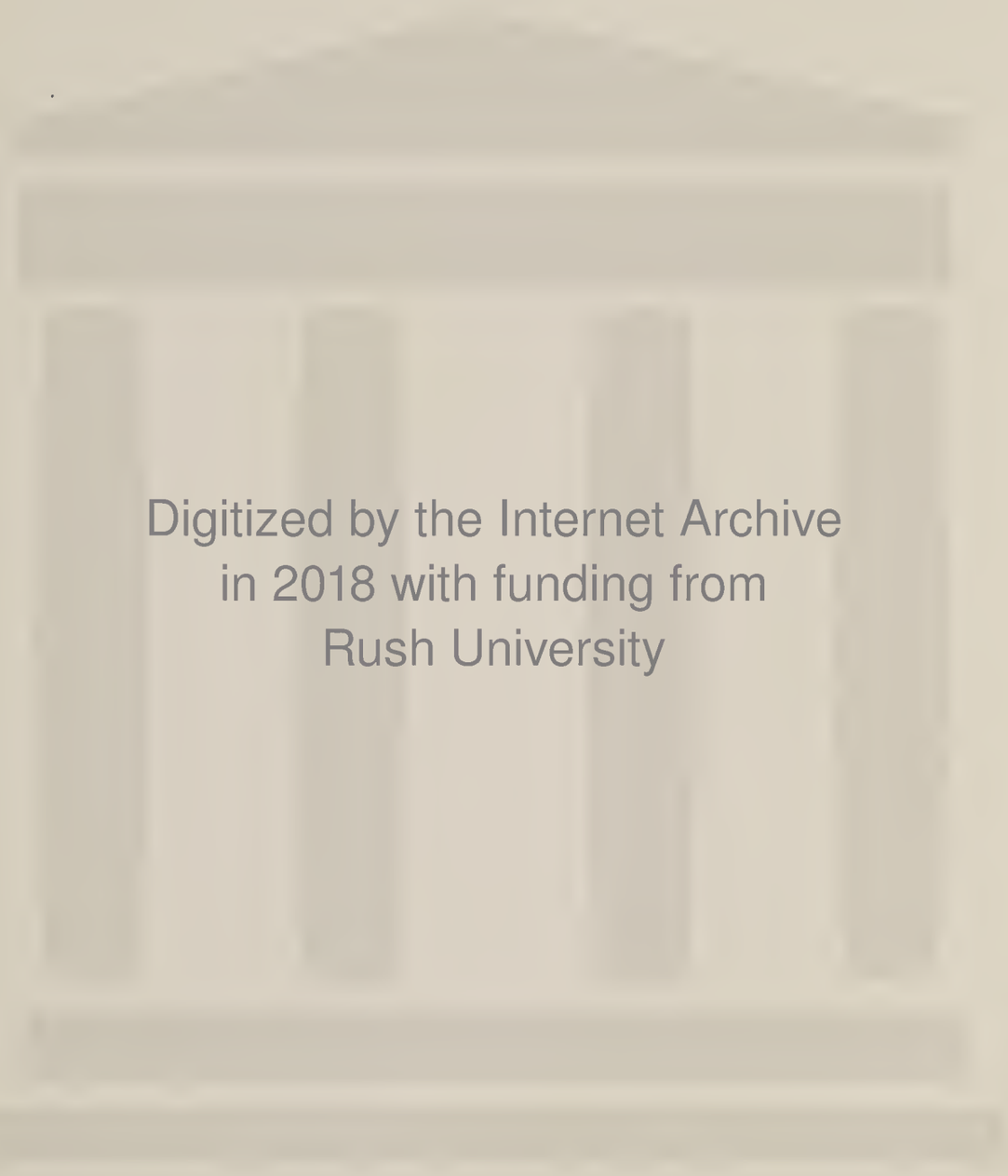

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CLINICAL ASPECTS OF MYOCARDIAL INFARCTION: I. USE OF ANTIARRHYTHMIC DRUGS

Philip R. Liebson

ABSTRACT. Rational use of antiarrhythmic drugs in acute myocardial infarction must depend upon the knowledge of the anatomy and physiology of the conduction system of the heart. Disorders of impulse initiation or conduction have been examined by increasingly sophisticated techniques using surface electrocardiogram, His bundle electrogram, and transmembrane potential studies. These studies have allowed evaluation of the mechanisms of arrhythmias, which may include changes of phase 4 depolarization of automatic fibers or variations in membrane responsiveness, resting membrane potential, and action potential duration due to hypoxia or local potassium imbalance. Quinidine, procainamide, lidocaine, diphenylhydantoin and propranolol are the most common antiarrhythmic drugs. These drugs may be classified on the basis of their actions on transmembrane potential of Purkinje fibers. Effects of these agents may be tempered by dosage, location of depressed myocardium, and abnormalities in metabolism and excretion of the agents due to decreased perfusion of liver and kidney. Because of effectiveness, rapidity of action and short plasma half-life, lidocaine is the drug of choice for potentially life-threatening ventricular arrhythmias in hospitalized patients after myocardial infarction.

INTRODUCTION

The development of continuous electrocardiographic monitoring of patients with myocardial infarction has led to a reduction in hospital mortality by 50 percent, primarily through the aggressive treatment of arrhythmias. Since most deaths from myocardial infarction ensue within a few hours after the acute attack, usually from ventricular fibrillation, it is possible that equally aggressive prophylactic antiarrhythmic therapy while the patient is still outside the hospital may reduce substantially the mortality from myocardial infarction.

Intelligent use of antiarrhythmic drugs requires a knowledge of the recent sophisticated evaluation of abnormalities in the cardiac conduction system leading to arrhythmias and the effects of antiarrhythmic drugs on electrophysiologic abnormalities. This is a review of some of the recent studies of cardiac conduction and the role of antiarrhythmic drugs in treatment of arrhythmias after myocardial infarction.

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ANATOMY AND ELECTROPHYSIOLOGY OF THE CARDIAC CONDUCTION SYSTEM

Anatomy

Electrophysiologic pacemaker function of the heart originates in the automatic fibers of the sino-atrial node in the right

atrium. Impulses generated here are conducted either through the "working," non-automatic atrial tissue or through preferential conduction paths of specialized fibers (internodal pathways) to the atrioventricular node.

The atrioventricular node is a bulbous interlacing of heterogeneous conduction tissue with variable automaticity. It consists of an upper ("A-N") region and a middle ("N") region with conducting but not automatic function, and a lower ("N-H") region which has both conducting and automatic function. A longitudinal arrangement of conducting fibers is found in the region from the A-V node to the His bundle ("H region"). Automaticity is found in conduction tissue below the "N" region of the A-V node. Below the His bundle, there is a trifurcation of specialized conduction fibers to form the right bundle, the left anterior bundle and the left posterior bundle (Fig. 1). These bundles terminate in small networks of fibers from which electrical impulses are conducted to the non-automatic "working" myocardial fibers.[1,2]

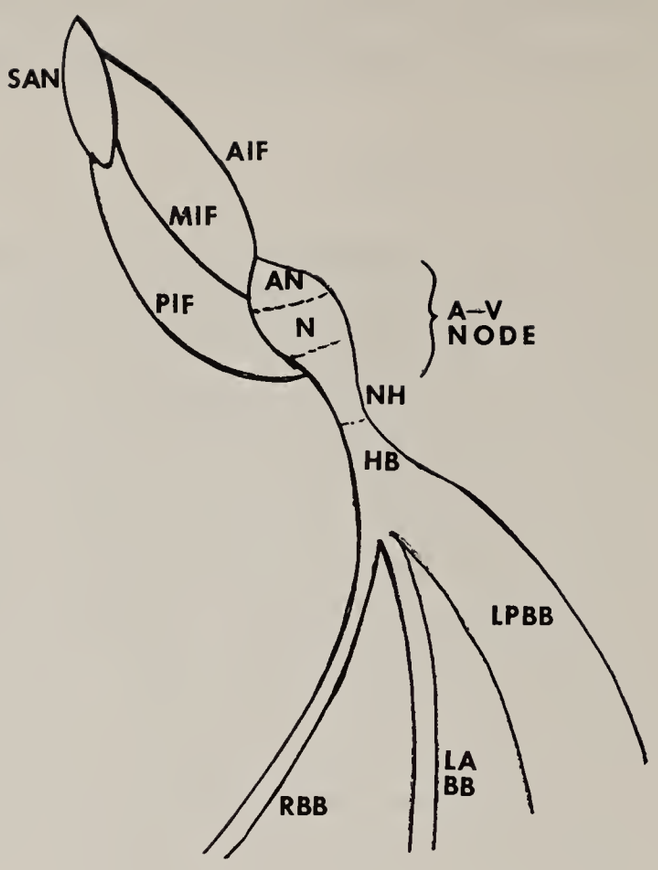

Fig. 1—Representation of specialized conduction system of the heart. SAN=sino-atrial node; AIF=anterior internodal fibers; MIF=middle internodal fibers; PIF=posterior internodal fibers; AN, N, N-H=regions of A-V node; HB=His bundle; LPBB=left posterior bundle branch; LABB=left anterior bundle branch; RBB=right bundle branch. Distal Purkinje system beyond bundle branches not shown.

Conduction can be determined by means of the surface electrocardiogram, His bundle recordings, and thin electrodes placed into specialized fiber pathways to record transmembrane potential.

The surface electrocardiogram allows determination of conduction time between the atrium and working myocardium of the ventricle. The P-R interval allows some gross evaluation of the conduction time between the upper A-V node and the working myocardium. The conducted impulse usually reaches the A-V node when the middle of the P wave is inscribed. The impulse has reached the working myocardium at the beginning of the QRS complex. The P-R interval, less 0.02 seconds, gives a reasonably good approximation of conduction from the upper part of the A-V node to the working ventricular myocardium.[3]

His bundle electrograms allow more definitive evaluation of conduction from the A-V junction to the ventricle.[3] This technique utilizes an electrode catheter placed transvenously with tip just beyond the tricuspid valve in the right ventricle. When the catheter tip is positioned correctly in apposition to the ventricular septum, recording at 6 to 8 times the normal electrocardiographic speed at 150 to 200 mm/sec with appropriate frequency, filtering will show three spikes on the His bundle electrogram. The first "A" spike is produced by right atrial depolarization just before the A-V junction. The second "H," or His, spike occurs when the impulse reaches the His bundle region. The third or "V" spike ensues when an impulse has reached working ventricular myocardium from the distal Purkinje conduction system. This technique shows that the normal interval from the upper A-V node to the working myocardium is approximately 150 msec (0.15 sec). The normal

A-H interval is approximately 100 msec, and the H-V interval is 40-60 msec. The latter interval allows estimation of conduction time in the bundle branch and His Purkinje system. Impulses in all three bundle branches must be slowed before the H-V interval increases.

It can be seen that the H-V interval could increase by 50 percent, for example, without an abnormally long P-R interval on the surface electrocardiogram (Fig. 2). Thus, His bundle electrocardiography is a valuable practical clinical tool for determining subtle conduction abnormalities.

The surface ECG and His bundle recordings reflect the action potentials of large numbers of cells, but a more specific evaluation of the response of specialized conduction tissue to antiarrhythmic agents may be made by evaluating single fiber transmembrane potentials.

ELECTROPHYSIOLOGIC PROPERTIES OF SINGLE FIBERS

Automaticity:

There are two types of cardiac tissue: automatic and nonautomatic. The single transmembrane potential of an automatic fiber demonstrates phase 4 diastolic depolarization; that of a nonautomatic fiber does not. When the membrane potential of an automatic fiber reaches the threshold potential, an action potential ensues. Automaticity may be decreased by (1) decreasing the rate of diastolic depolarization; (2) increasing the threshold potential; or (3) increasing the maximum diastolic potential (Fig. 3).[4,5]

Automaticity may be varied by changing impulses from autonomic nerves and by local changes in extracellular potassium, pH, pO_2, and possibly by extracellular concentration of calcium ions. The most likely determinant for the normal diastolic depolarization during phase 4 is potassium efflux.[1]

Both automatic and nonautomatic cells share similar responses other than spontaneous phase-4 depolarization.

Conduction:

The velocity of conduction in all cardiac fibers is determined by (1) the magnitude of the resting potential at time of depolarization; (2) the rate of rise of phase 0 of the action potential; (3) the threshold potential of the cardiac fiber (Fig. 4).[4]

An impulse that causes depolarization from an increased resting potential related to a given threshold potential will produce

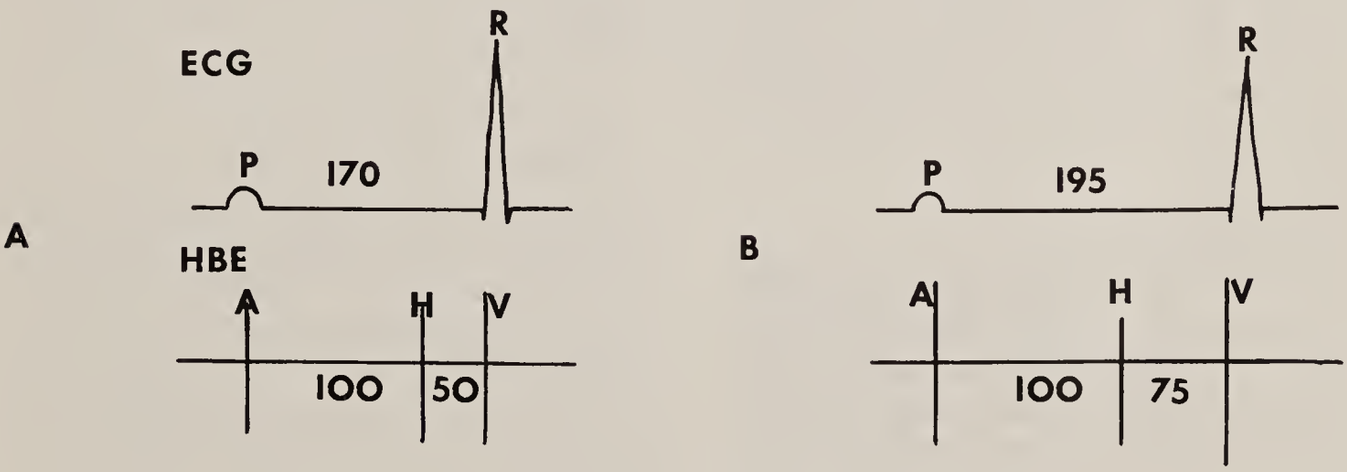

Fig. 2—Relationship of surface electrocardiogram (ECG) to His bundle electrogram (HBE). *Panel A* represents a normal set. P-R interval of ECG is 170 msec. A-V interval is 150 msec. Note that A falls in the middle of the P wave. H=His bundle depolarization. *Panel B* demonstrates a 50 percent increase in the H-V interval (from 50 to 75 msec) due to block in all three bundle branches. P-R interval, though slightly increased from A, is still within "normal limits."

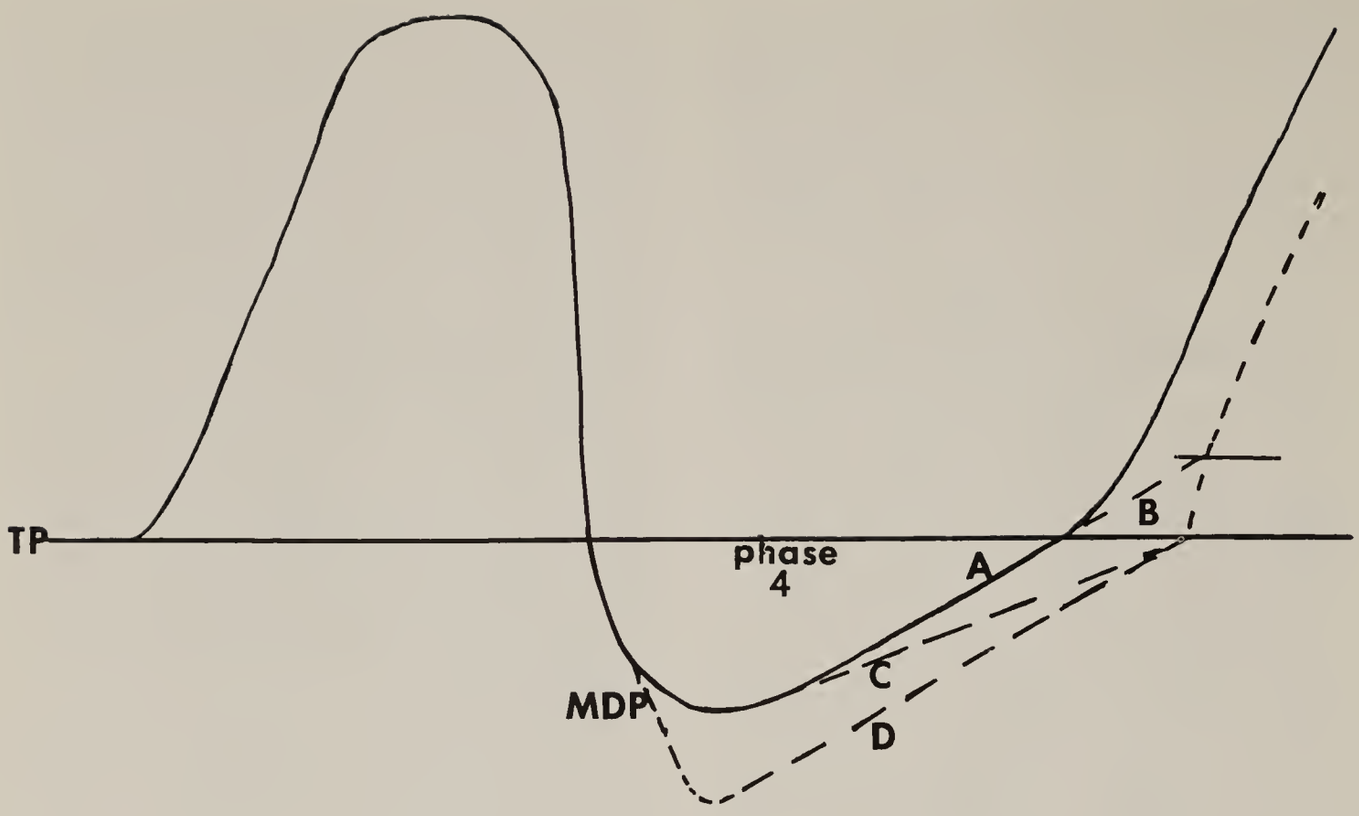

Fig. 3—Pacemaker fiber action potentials showing causes of decreased phase 4 diastolic depolarization, thus decreasing automatic rate. TP=threshold potential; MDP=maximal diastolic potential; A=control; B=effect of increase in threshold; C=effect of decrease in rate of depolarization; D=effect of increase in maximal diastolic depolarization (Modified from Lown et al.[5]).

a greater rate of rise of phase 0 of the transmembrane action potential, thus leading to an increased conduction velocity.[4]

Membrane Responsiveness:

Membrane responsiveness defines the maximal rate of rise of phase 0 from a given resting membrane potential. Antiarrhythmic drugs may affect conduction by their effect on membrane responsiveness (Fig. 5).

Refractoriness:

The refractory period of a cardiac fiber lasts until a time after the beginning of the action potential when another stimulus can cause a second action potential.[5] The earliest prematurely induced action potential which is able to propagate along the fiber bundle defines the effective refractory period. Usually, the cell again becomes responsive when the transmembrane potential is greater than the threshold potential, but the recovery of excitability may be much later.

THE DEVELOPMENT OF CARDIAC ARRHYTHMIAS

Arrhythmias involve abnormalities in the regular rhythm of the heart. These result from abnormalities in (1) impulse initiation or (2) impulse conduction, or both.

Impulse Initiation Disorders (Changes in Automaticity)

These abnormalities may result from an increase in automaticity of a subsidiary pacemaker to a point where its rate is faster than that of the previous pacemaker. Thus, if the rate of a pacemaker in the A-V junction becomes greater than that of the SA node, an A-V dissociation with junctional tachycardia might ensue.

On the other hand, if the sinus node automatic rate decreases considerably, it may fall below that of the usual rate of a subsidiary pacemaker and, similarly, an A-V dissociation might ensue, but in this case with a junctional rhythm which is

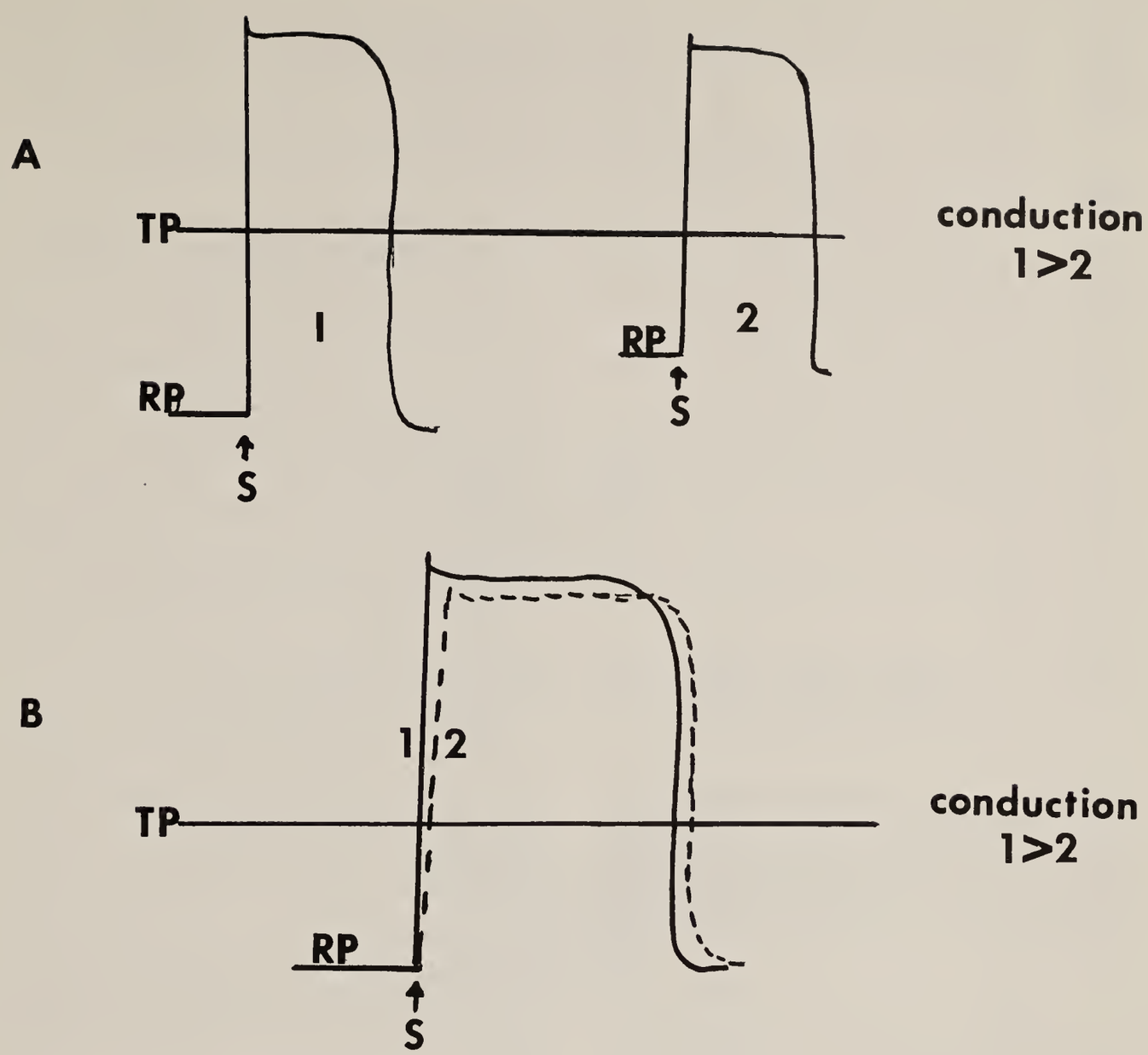

Fig. 4—Causes of change in conduction velocity. *Panel A*=lower resting potential (RP) at time of stimulus (S) causes decreased rate of rise (phase 0) of action potential and decreased conduction velocity (2 less than 1). *Panel B*=increased membrane responsiveness causes a faster rate of rise of phase 0 from the same resting potential (RP) and an increased conduction velocity (1 has greater membrane responsiveness than 2). TP=threshold potential.

not rapid. Increased automaticity of distal Purkinje fibers with variable degrees of entrance and exit block to these areas might lead to parasystolic beats. The latter are diagnosed by variable coupling time with normal QRS complexes and intervals between parasystolic QRS complexes which are multiples of the smallest parasystolic R-R interval.

Impulse Conduction Disorders

Conduction may be decreased by diminishing membrane responsiveness or varying membrane potential when the fiber is stimulated, both of which affect the rate of rise of phase 0 of the action potential.[1,5] Studies with isolated canine Purkinje fibers have demonstrated that impulses may be slowed down by a factor of over 40 by increasing local potassium concentration extracellularly.[1,6] The slowing of conduction may cause a unidirectional block; that is, a block of conduction in one direction without a complete block in the other direction.[6] Thus, if impulses from two directions enter this depressed block of fibers, the anterograde impulse may be blocked completely, and

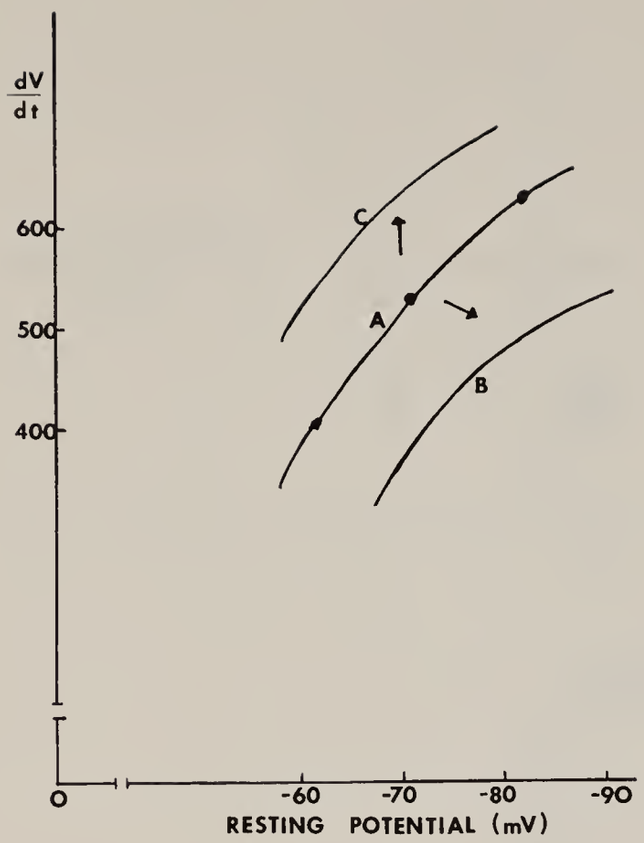

Fig. 5—Curve of membrane responsiveness. A shows control curve of rate of rise of action potential from a given resting potential. Decreased membrane responsiveness would shift curve to right (B). Increased responsiveness would shift curve to left (C) (Modified from Lown et al.[5]).

the retrograde impulse may be slowed, but not completely blocked. The retrograde impulse finally could leave the depressed area and enter normal tissue after the normal tissue has regained its excitability from the previous impulse, producing a reentry extrasystole (Fig. 6).

Theoretically, antiarrhythmic drugs with opposite effects on conduction could cause decreased reentry. A drug which increases conduction might allow the initial impulse to enter the depressed segment in an anterograde direction for a longer distance, thus making more fibers refractory. When the reentry impulse moves retrogradely from the other side, it is thus more likely to be blocked due to refractory tissue from the anterograde impulse, and exit out of the depressed area would be blocked (Fig. 6).[7]

On the other hand, decreasing conduction velocity might prevent the reentrant retrograde impulse from ever getting out of the depressed area, even if the anterograde impulse does not penetrate too far. Thus, opposite effects on conduction achieve the same result: decreased reentry and decreased extrasystoles (Fig. 6).

ELECTROPHYSIOLOGIC EFFECTS OF ANTIARRHYTHMIC DRUGS

The antiarrhythmic agents most commonly used include quinidine, procainamide, lidocaine, diphenylhydantoin (Dilantin,® hereafter referred to as DPH), and propranolol. In this section we will consider and compare their actions on Purkinje fibers. The cardiac glycosides are not regarded as primarily antiarrhythmic agents and will not be discussed here.

All five agents decrease automaticity of Purkinje fibers by decreasing the rate of phase 4 depolarization (Table I).[4,8-10]

Aside from automaticity, other effects on the membrane differentiate the properties of antiarrhythmic drugs. Various classifications have been made of antiarrhythmic drugs based upon (1) action potential amplitude, (2) maximal slope of phase 0 depolarization, (3) membrane responsiveness, (4) conduction velocity, (5) action potential duration, (6) sympathetic blockade, and (7) effects on inward calcium current.[4,11]

The Hoffman-Bigger classification differentiates two classes of drugs on the basis of effects on action potential amplitude, maximal slope of phase 0 depolarization, membrane responsiveness and conduction velocity.[4] *Class 1* includes quinidine, procainamide and propranolol. *Class 2* includes lidocaine and diphenylhydantoin. *Class 1* drugs decrease all four determinants. *Class 2* drugs have variable effects. Lidocaine and DPH cause no change in action potential amplitude and variable effects on the other three factors, depending upon concentration of the drug and status of depression of the tissue evaluated.[4,12] Action potential duration is increased by quinidine and procainamide, and decreased by propranolol, lidocaine and DPH, so that propranolol has a property similar to the *Class 2* group in this respect (Table I).

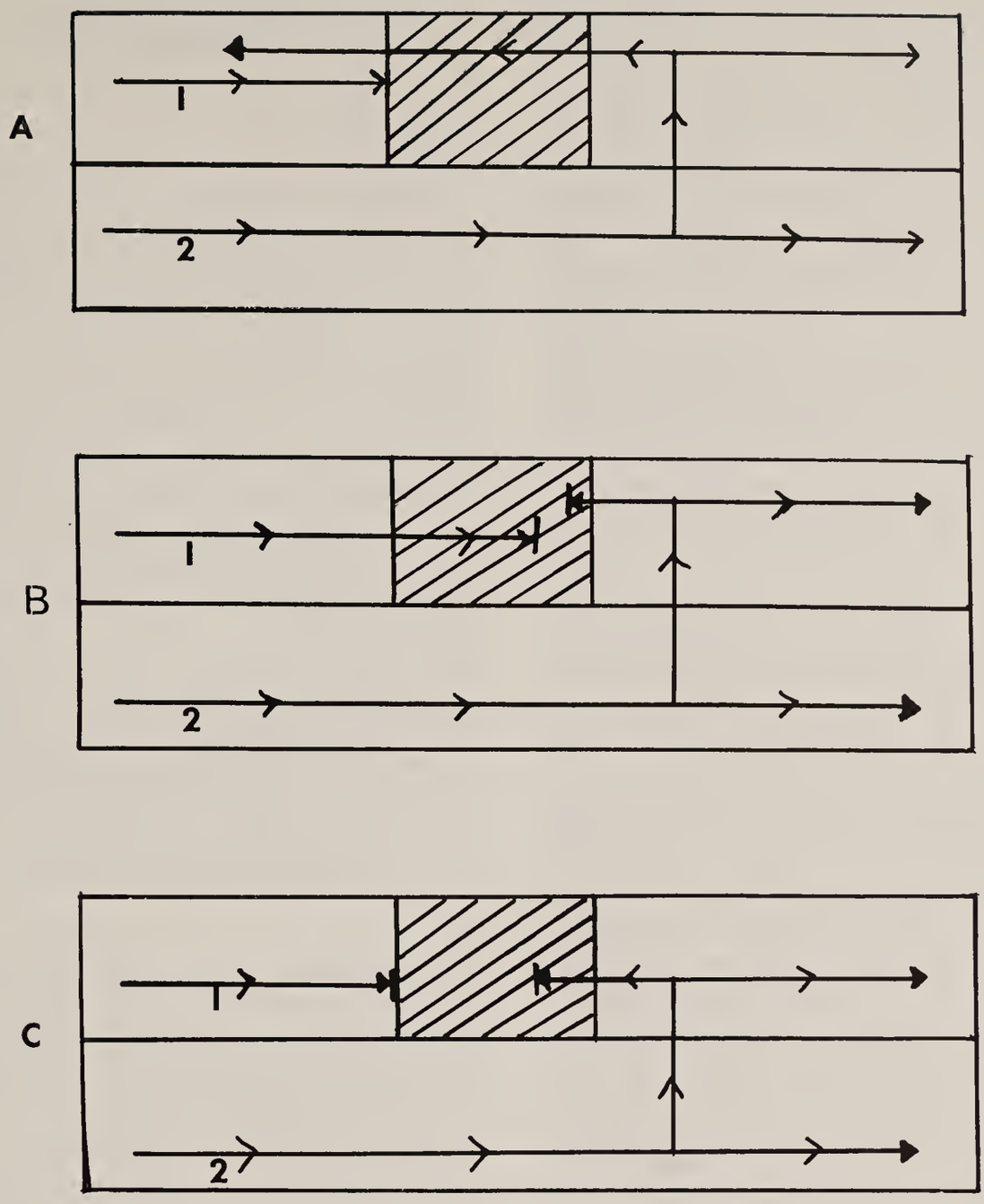

Fig. 6—Schematic representation of reentry. Panel A shows two impulses conducting anterograde (left to right) parallel to one another. Impulse 1 is blocked at the beginning of a depressed area (diagonal lines). Impulse 2 reenters area from opposite direction and exits in a retrograde manner (right to left) if fibers ahead of it are capable of depolarization. Panel B shows effect of an antiarrhythmic agent which could prevent reentry by increased conduction of impulse 1 into depressed area to a point where the increased depolarization could block the reentry of impulse 2. Panel C shows the effect of an antiarrhythmic agent which could prevent reentry by decreasing retrograde conduction of impulse 2 (Modified from Cranefield et al.[1]).

The consequences of these actions lead to significant decreases in conduction velocity, especially with procainamide and quinidine. This produces prolonged QRS complex and Q-T intervals on electrocardiogram with toxic doses of these agents, but this effect does not occur with propranalol, DPH, or lidocaine.

Ideally, if one could demonstrate in any individual patient a specific localized abnormality, it might be possible to determine precisely a rational approach to antiarrhythmic therapy. The demonstration of low resting potentials and small action potentials in Purkinje fibers could be responsible for parasystolic firing in the area, with associated decreased conduction velocity and the possibility of reentry. A

drug which decreased automaticity and responsiveness of partially depolarized cells could decrease these arrhythmias (procainamide). On the other hand, some action potentials may have a normal amplitude but long duration, leading to temporal dispersion of action potential durations in a small area of fibers, causing reentry. Temporal dispersion refers to variation of action potential duration of fibers in an area leading to different rates of recovery of excitability. Reduction in action potential duration by DPH for example, could possibly reduce temporal dispersion of action potentials and prevent reentry.

It must be emphasized that action of an antiarrhythmic drug on one type of conduction fiber may allow an imprecise prediction of the effect of an agent in a general clinical situation. Important in the use of an agent is consideration of (1) differing effects of drugs on one type of tissue with large or small doses; (2) changes in local ionic and oxygen concentrations, (3) differing actions of an agent on cardiac muscle in different areas of the heart. It is also important that, if possible, plasma drug levels be known because of possible differences of absorption and metabolism of the same dose/kg in different individuals. These considerations will be emphasized below in our evaluation of individual antiarrhythmic drugs.

SPECIFIC USES OF ANTIARRHYTHMIC DRUGS

Quinidine

Quinidine, the dextro-isomer of quinine, is the oldest antiarrhythmic drug of the five discussed here. Before the 1950's, it was the mainstay of therapy in the abolition of ventricular tachycardia. When given in a situation of acute myocardial infarction, it can significantly decrease premature ventricular contractions, serious ventricular arrhythmias, multi-focal ventricular premature contractions, consecutive ventricular premature contractions and premature supraventricular contractions.[13,14]

It acts by depressing diastolic depolarization of Purkinje fibers, by decreasing conduction in the atrium, specialized conduction system and ventricles, and by prolonging the refractory period of atrial ventricular and specialized conduction system.[4]

Quinidine should be used with caution in atrial flutter because its vagolytic effect might decrease A-V block and suddenly increase the ventricular rate, with markedly adverse results, especially in myocardial infarction. Therefore, digitalis, which blocks A-V conduction, is useful to insure a reasonable amount of block to

TABLE I

EFFECTS OF ANTIARRHYTHMIC DRUGS ON PURKINJE FIBER ACTION POTENTIALS*

AGENT	AUTOMATICITY (Diastolic Depolarization)	CONDUCTION (Membrane Responsiveness)	CONDUCTION (Conduction Velocity)	REFRACTORINESS (Action Potential Duration)
		Class 1		
Quinidine	Decreases	Decreases	Decreases	Increases
Procaineamide	Decreases	Decreases	Decreases	Increases
Propranolol	Decreases	Decreases	Decreases	Decreases
		Class 2		
Lidocaine	Decreases	No Change	No Change	Decreases
Diphenylhydantoin	Decreases	Increases in depressed fibers	Increases in depressed fibers	Decreases

*Modified from Hoffman-Bigger classification

prevent this adverse effect while attempting to convert atrial flutter to sinus rhythm by the use of quinidine.

When given orally, it is almost completely absorbed, and drug levels appear in the blood in 15 minutes, with peak levels in 1 to 3 hours and plasma half-life of approximately 6 hours. Quinidine is hydroxylated by the liver, and its metabolic product is excreted by the kidney. Therapeutic levels are approximately 2 to 8 mg/liter (Table II).[10,15]

Aside from its adverse effects of hypotension and cinchonism, quinidine is especially potentially hazardous in patients with myocardial infarction because it depresses myocardial contractility, although, in small doses, it may actually increase contractility.[10,16] It should be used with caution, if at all, in patients with A-V block. The use of quinidine by the intravenous route is associated with a high incidence of adverse reactions, such as hypotension and ventricular fibrillation.

Procainamide

Procainamide has effects similar to that of quinidine, but its half-life in plasma is shorter (2½ to 4½ hrs.) and its effect begins sooner.[17] To achieve therapeutic levels (4 to 8 mg/liter) an intramuscular priming dose of 750 to 1000 mg may be given at the same time as an oral dose of 500 mg. Peak concentration can be reached in 25 minutes. With no priming dose and repeated oral doses every three hours, therapeutic levels will be reached usually in 6 to 8 hours. Oral therapy must be repeated every 3 to 4 hours to keep plasma levels in therapeutic range (Table II).

Oral absorption may vary considerably from 75 to 95 percent.[17] Most of the procaineamide absorbed is excreted in the urine (60 percent), and it is partly hydrolyzed in the plasma.[10] There is considerable variation, among individuals, of plasma levels with a given dose based on body weight. Plasma levels are needed to determine therapeutic range once a stable dose has been reached.

Procainamide is quite useful in definitive treatment of ventricular arrhythmias in the acute infarct period.[18,19] Long-term use of procaineamide for prophylactic antiarrhythmic therapy has been disappointing. Lown and his group found that 14 of 16 patients receiving the drug for periods longer than three months after a myocardial infarction had late reactions, necessitating discontinuance of the drug.[20] Periodic monitoring of electrocardiograms showed that in the procainamide-treated group there was no decrease in frequency of premature ventricular beats compared with control groups. There were fewer sudden deaths in the treated group, though

TABLE II

PHARMACODYNAMICS OF ANTIARRHYTHMIC DRUGS: DOSAGE, PLASMA LEVELS, AND FATE

DRUG	ADMINISTRATION	USUAL DOSAGE (mgm)	PLASMA T ½ (Hours)	THERAPEUTIC PLASMA LEVELS (mgm/L)	FATE
Quinidine	Oral	100-400 q.i.d.	6	2-8	Metabolized in liver
Procaineamide	Oral	Initial Dose: 500-1000 q 3hr: 250-500	2.5-4.5	4-8	60% excreted in urine Hydroxylated in plasma
Lidocaine	IV	1/kg IV Bolus 1-4/min infusion	9 min.*	1.5-6.0	Metabolized in liver
Propanolol	Oral	10-80 q.i.d.	3	20-40	Metabolized in liver
	IV	10 (1/min)	8 min.* 2½**	20-40	Metabolized in liver
Diphenylhydantoin	Oral	100-200 t.i.d.	46	10-20	Metabolized in liver
	IV	100-300 (100/5 min)	4-6	10-20	Metabolized in liver

*First phase **Second phase

Abbreviations: IV = introvenous; T ½ - half-time' mgm/L = milligrams per liter

this decrease was not statistically significant. Many patients treated with procaineamide for one year develop antinuclear antibodies and some develop lupus erythematosus-type syndromes. Both these effects are reversed after stopping medications.[21,22]

Thus, although procainamide is a potentially effective drug when given in the situation of acute myocardial infarction where patient monitoring is possible, its potential toxicity and its inconclusive effect in decreasing long-term arrhythmias precludes widespread use in patients outside the hospital.

Lidocaine

This is the drug of choice for rapid abolition of life-threatening ventricular arrhythmias. Its effects on the Purkinje fiber are different from those seen in the procainamide-quinidine group, although it similarly decreases diastolic depolarization. However, it shortens the action potential of Purkinje and ventricular fibers. It has less adverse effect on contractility than procaineamide and quinidine. It has little effect on SA node, atrial tissue and, thus, has little use in supraventricular tachycardias.[4,10,23,25]

In the Medical Intensive-Coronary Care Unit of Presbyterian-St. Luke's Hospital, lidocaine is given by IV bolus in the following situations of ventricular arrhythmias in patients with possible myocardial infarction: (1) ventricular tachycardia; (2) 6 unifocal ventricular premature beats per minute; (3) one or more sets of multifocal ventricular premature beats; (4) couplets (two successive ventricular extrasystoles; (5) ventricular extrasystole seen in the vulnerable period of the previous normal systole (R-on-T).

Lidocaine is given as an IV bolus in a dose of 1 mg/kg followed immediately by an intravenous infusion of from 1 to 4 mg per minute to maintain therapeutic levels. Its maximal electrophysiologic effect is achieved within 30 seconds. It is rapidly metabolized by the liver, its plasma half-life being increased in liver disease and in situations where cardiac output is diminished (congestive heart failure, cardiogenic shock).[26] In these circumstances caution should be used that lidocaine not be given in too high dosage. Effective therapeutic levels are between 2 to 5 mg/l in plasma. Toxicity leads to central nervous system symptoms (Table II).[10]

Because of extremely high mortality in the first few hours after a myocardial infarction, usually from ventricular fibrillation, studies of the efficacy of intramuscular lidocaine in producing therapeutic levels have been accomplished. With high dose intramuscular injection (6 mg/kg) into the deltoid region, lidocaine levels in the plasma persisted in high therapeutic range for over 30 minutes, with maintenance of therapeutic levels for two hours.[27] Minor side effects occurred in 50 percent, but "no major neuro-toxicity" was reported. Thus, intramuscular lidocaine may have some future place in prophylaxis against arrhythmias in the pre-hospital phase of myocardial infarction.

Diphenylhydantoin (DPH, Dilantin®)

Diphenylhydantoin behaves like lidocaine on Purkinje fiber action potentials, in contrast to the quinidine-procainamide group. Recent studies have shown that some of the properties of the lidocaine-DPH group (i.e., little effect on maximal rate of depolarization in contrast to a reduction in the procaineamide-quinidine group) may be related to extracellular potassium and that with higher extracellular potassium; lidocaine-DPH can produce a similar depression of maximal rate of depolarization.[11] This may be the situation in areas of ischemic myocardium. Thus, DPH especially may have contrasting effects on membrane responsiveness, maximal slope of phase 0 depolarization and conduction velocity, depending upon therapeutic dose and state of extracellular potassium.[4,11,28]

It has been useful in digitalis toxicity to reduce ventricular extrasystoles, ventricular tachycardia, or paroxysmal atrial tachycardia with block.[29,30] It has less effect on atrial and ventricular arrhythmias not induced by digitalis. It may be given orally

or intravenously; but by the latter route, there is a serious possibility of hypotension due to the diluent (ethyl alcohol and propylene glycol). The diluent has also been found to cause an increase in threshold current required for any given stimulous, an effect antithetical to that of DPH itself.[8]

When given intravenously, usually as a 50 to 100 mg dose over 10 minutes, its half-time in plasma is 4 to 6 hours (Table II). Therapeutic plasma levels vary between 10 to 18 mg/l.[29,31] DPH is metabolized in the liver. Its side effects include hypotension, gastrointestinal symptoms, gingival hyperplasia, ataxia and megaloblastic anemia.

Propranolol

This is the first beta-blocking agent to be used widely, both for its antiarrhythmic effect and to decrease ischemic pain. It is a competitive antagonist of isoproterenol. Conduction velocity is decreased in many parts of the heart, and propranolol is useful in conversion of atrial arrhythmias induced by digitalis.[32] Propranolol and quinidine have similar antiarrhythmic properties, and combinations of the two drugs may be useful in situations where too much of one drug may lead to side effects.[33] Such a situation might be one in which atrial flutter or fibrillation is to be terminated by such a combination. Propranolol might also be useful in combination with relatively low doses of digitalis for producing A-V block in atrial fibrillation, thereby modifying the ventricular response to a reasonable rate. This might be useful in renal disease where digoxin levels may rise considerably if the usual dose of this agent is given.

For rapid effect, propranalol may be given in a 10-mg intravenous dose at a rate of 1 mg/minute. It is rapidly metabolized by the liver (Table II).

Propranolol does not inhibit the positive inotropic effect of digitalis on the myocardium and, in this context, it may be useful in combination with digitalis in arrhythmias associated with myocardial depression. It should not be given, however, in overt congestive heart failure, or in patients with bronchial asthma.[34]

Its beta-adrenergic blocking effects include slowing of the sinus rate and decreased A-V conduction. These are of minor importance in its use as an antiarrhythmic, especially in reference to digitalis toxic rhythms. Treatment of the latter depends upon a membrane effect similar to that of quinidine, which appears to be unrelated to its beta-blocking effect.

SUMMARY

In summary, the use of antiarrhythmic agents, especially in the situation of acute myocardial infarction, must be tempered by the knowledge of variable and unpredictable effects in the face of different extracellular potassium concentrations and location and degree of myocardial depression. The effect of the diminished cardiac output on drug metabolism and excretion must also be considered. Lidocaine is the drug of choice for rapid suppression of life-threatening ventricular arrhythmias in myocardial infarction. Supraventricular arrhythmias may respond to digitalis (not discussed in detail here), quinidine, propranolol, or combinations of these drugs. Procainamide and quinidine are useful in definitive in-hospital therapy of ventricular arrhythmias after myocardial infarction, but have questionable efficacy in widespread long-term use. DPH may have a special place in treatment of digitalis toxic arrhythmias, but must be used with caution because of the hypotensive effect of its diluent. Careful attention to maintaining adequate arterial oxygenation, electrolyte balance and renal output may be of as much use in preventing arrhythmias as the use of antiarrhythmic agents.

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CLINICAL ASPECTS OF MYOCARDIAL INFARCTION: II. SHOCK AFTER MYOCARDIAL INFARCTION

PHILIP R. LIEBSON

ABSTRACT. As a result of increased arrhythmia surveillance in coronary care units, hospital mortality rate from myocardial infarction has decreased from 35 percent to between 15 and 20 percent. Cardiogenic shock is now by far the most common cause of death from myocardial infarction in patients treated in a coronary care unit. Little advance has yet been made in decreasing the mortality rate of 70 to 90 percent in cardiogenic shock. Although earlier studies using inotropic agents such as levarterenol and isoproterenol suggested that mortality might be decreased by their use, more recent evaluation, using stricter criteria for diagnosis of cardiogenic shock, has indicated that they have no major effect on prognosis. Shock may respond frequently to pharmacologic intervention should it be due to hypovolemia, indicated by low central venous or pulmonary capillary wedge pressure. In this situation, use of plasma expanders or 5 percent dextrose/water may reverse the shock state in a considerable proportion of patients.

In situations where hypovolemia is not a factor in shock (true pump failure), use of intra-aortic counterpulsation assist devices have had a significant transient effect of reversing the shock syndrome and stabilizing the patient to allow for emergency coronary angiography and left ventriculography. Although mortality has not decreased remarkably by use of intra-aortic assist alone, the combined use of early intra-aortic counterpulsation assist and coronary by-pass surgery in selected patients might increase survival.

INTRODUCTION

Shock after myocardial infarction is a clinical state in which there is severe failure of the left ventricle as a pump, associated with high mortality. The syndrome is characterized by hypotension, pallor, peripheral coolness and moistness, obtundation and decreased urinary output.[1] It is the most common cause of death from myocardial infarction in a coronary care facility, and its fatality rate is between 70 and 90 percent without therapeutic intervention.[2-4] It must be differentiated from other causes of "cardiogenic shock" associated with post-surgical pump bypass conditions, or severe valvular heart disease, and also differentiated from the general term "circulatory shock" which may be due to hemmorhage, gram negative sepsis, or severe volume depletion.[5]

Since James Bryan Herrick referred to myocardial infarction shock in his classic paper in 1912 (he referred to it as "collapse"), this syndrome has intrigued clinicians.[6] Over the past decade, with the proliferation of coronary care units and bedside hemodynamic and metabolic studies, much insight has been gained into the functioning of the heart in the shock state. Although treatment of myocardial infarction shock has not led to a marked decrease in mortality, application of me-

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chanical cardiac assist devices has temporarily decreased morbidity in a significant number of patients.

This review of shock after myocardial infarction will examine techniques for evaluating this syndrome and the rationale for and against specific therapeutic interventions.

CLINICAL EVALUATION OF THE PATIENT WITH CARDIOGENIC SHOCK AFTER MYOCARDIAL INFARCTION

Historical Prespectives

Myocardial infarction as a discrete clinical entity was not widely diagnosed until the late 1920's, when the electrocardiogram became widespread.[1] It was only after 1940 that full 12-lead recordings allowed more comprehensive diagnosis of infarction.[8] Serum enzyme determinations were used to establish definitive diagnosis after 1950.[9]

The development of cardiogenic shock after myocardial infarction was recognized for many decades as a phenomenon associated with hypotension, decreased urine output, decreased mentation and peripheral sympathetic signs. The syndrome was regarded as almost inevitably fatal, and, before 1950, treatment consisted of coronary dilator drugs, sedation and oxygen.[10,11] The shock syndrome was believed by many to be a compensatory phenomenon which reduced the work of the heart and, therefore, should not be treated.[10,12]

Advances in the therapy of myocardial infarction shock came with successful development of an animal myocardial infarction model in the early 1950's.[13,14] Within the next decade, a wide variety of drugs, mainly vasopressors and inotropic agents, came into general use for the treatment of shock, with variable success.[15-18]

Although Forssman, with the cold objectivity of scientific pursuit, inserted a catheter into one of his peripheral veins and threaded it into his own right atrium in 1929,[19] it was only in the 1960's that bedside catheterization of patients with myocardial infarction became commonplace, and not until the late 1960's that clinical examination of left ventricular function by bedside techniques became accepted as a reasonably safe procedure for determining the severity of myocardial infarction.[20,21] This approach provides indispensible information for the purpose of deciding upon appropriate therapy.

Over the past five years, bedside catheterization has classified the hemodynamic and metabolic function of the left ventricle in myocardial infarction shock.[22,23] Its use in conjunction with intra-aortic phase shift balloon assist or external counterpulsation devices has afforded a means of temporarily stabilizing a shock patient.[24,25] Most recently, the early decision for emergency coronary artery by-pass surgery in patients showing no reversal of the shock state after short periods of counterpulsation assist has produced some decrease in mortality in this highly selected group of patients.[26]

CLINICAL ASPECTS OF CARDIOGENIC SHOCK

Patient History

Attempts to predict the development of cardiogenic shock in patients with myocardial infarction on the basis of age, sex and past history, have reported conflicting results. Nielsen and Maruer found that the proportion of patients with shock relative to those with myocardial infarction was the same in men and women: approximately 10 percent.[27] Their study indicated that the incidence of previous infarction was slightly higher, though not significantly so, in those developing shock than in the non-shock patients. A more recent study, based upon stricter criteria for cardiogenic shock, demonstrated no difference in the proportion of patients developing shock who had had previous infarcts.[4] The proportion of women with myocardial infarction developing shock

was higher than that of men.[4] Hypertension and diabetes have been found in a higher proportion of shock than in non-shock patients with infarction, but more recent studies show no such correlation.[4,28] Since myocardial infarction may be a complication of hemorrhagic shock or other forms of hypotension, strict criteria for cardiogenic shock after myocardial infarction must be considered to determine the possible implication of past history in the development of the clinical syndrome.

Clinical Profile

Two patterns of clinical course have been noted by Swan *et al*, in the setting of shock after myocardial infarction.[1] Young patients with first infarcts may die within minutes or hours after severe circulatory collapse and hypotension. In older patients with previous infarcts, unexpected cardiac arrest and extension of infarct may occur, with slow deterioration. The development of shock after the initial acute infarct event usually occurs within 24 hours.[4] Approximately 50 percent of patients are dead within 10 hours from shock onset.

Although arrhythmias and heart block are frequent in cardiogenic shock, most patients are in normal sinus rhythm or sinus tachycardia at the time the shock syndrome develops.[4] In patients with anterior wall infarcts, the development of complete heart block presages the development of shock since extensive involvement of left ventricular myocardium is associated with this form of heart block.[29,30,31] The development of shock with complete heart block after inferior wall infarction is much less frequent, since a more focal lesion in the conduction system is usually associated with this type of infarction.[32] It is much more difficult to treat life-threatening arrhythmias during the shock state than in an uncomplicated infarction. Efforts at resuscitation after ventricular tachycardia or ventricular fibrillation in the setting of cardiogenic shock are usually unavailing.[33,34]

PATHOLOGIC CORRELATIONS

Necropsy studies of patients with cardiogenic shock show that anterior wall involvement is greater, but so is the general incidence of anterior wall versus posterior or inferior wall involvement in myocardial infarction.[4,27] At least 30 percent of the left ventricular myocardium, including the septum, is involved.[35–37] Patients dying immediately after myocardial infarction without shock (intractable arrhythmias, ventricular rupture) invariably have less than 35 percent of the myocardium involved.[36]

Evidence for extension of infarction is found in a majority of patients dying of cardiogenic shock,[36,37] by the presence of areas of patchy necrosis not found in patients without shock. The patchy necrosis is usually found around the borders of the major infarct area, and averages six percent of the left ventricular mass.[36]

Although there is little question that shock is related to total myocardium infarcted, there is controversy about whether specific infarct areas produce special vulnerability to shock. All patients in one study had involvement of the apical region.[36] In another study, those who developed sudden ventricular fibrillation after infarct and did not survive resuscitation attempts, quite commonly had anterior infarcts with septal involvement and conduction defects.[38] In patients with cardiogenic shock undergoing emergency coronary angiography and left ventriculography, 70 percent had dyskinesis or akinesis of the anterolateral wall and apex.[26] Cardiogenic shock was rarely found in patients with subendocardial (non-transmural) infarcts.[39] The occurrence of a previous infarct, however, would have considerable bearing on the development of shock after a fresh, non-transmural infarct.

Post-mortem study of coronary arteries shows that total coronary occlusion is not necessary for infarcts, but that over 75 percent occlusion by plaques is usually found in involved arteries.[40] Coronary thrombi occur in only 10 percent of patients dying suddenly or with subendo-

cardial infarcts. They occur in 50 percent of those dying with transmural infarcts without shock or severe failure, and in higher percentages in those with cardiogenic shock or congestive heart failure. Approximately 45 percent of patients undergoing emergency coronary arteriography in cardiogenic shock had three-vessel disease, and the left anterior descending coronary artery was always invovlved.[26]

Studies of animal models with cardiogenic shock after myocardial infarction show that shock syndrome appears to be greater with primary branch occlusions than with mainstem occlusion.[41] Branch occlusion in the circumflex artery distribution was highly associated with shock. Microspheres, which occlude coronary artery branches rather than mainstem vessels, more likely produce shock in experimental models. In one clinical study, 12 of 16 patients with branch occlusions had cardiogenic shock after myocardial infarction with relatively frequent involvement of the left circumflex artery branches.[41] Conversely, only 25 percent with cardiogenic shock had branch occlusions. It was postulated by the authors that receptors at the right angle branches of the major coronary arteries may set up reflexes which produce shock when these branches are occluded.

Mortality rates for cardiogenic shock after myocardial infarction were reviewed in 1960, and varied widely in different studies, between 14 and 100 percent, due to inconsistent criteria for shock.[42] Current studies based upon strict criteria place mortality at 75 to 90 percent.[4,43]

In summary, although special locations of coronary occlusion and specific areas of the left ventricle may be more commonly defined in patients dying of shock, the best correlations involve extent of old and recent infarction and the presence of three-vessel coronary artery disease.

QUANTIFICATION OF INFARCT SIZE

If it is accepted that extent of infarct correlates with the development of cardiogenic shock, it would be important to quantify infarct size *in vivo* to predict development to this syndrome. Infarct size can be determined by serum creatine phosphokinase (CPK) activity and isoenzyme profile.[44-49] Serial two-hour measurement of plasma CPK allows comparison with an equation which accounts for CPK distribution space, fractional disappearance rate, proportion degraded by myocardium, and proportion released into the circulation.[46,49]

Because of the scatter of data, peak CPK *per se* cannot be used precisely to define infarct size, although high peak CPK values are generally correlated with higher mortality.[46] Peak CPK depends upon rate of enzyme release and may not indicate small extensions of the initial infarct. Changes in serum lactic dehydrogenase and glutamic oxaloacetic transaminase activity depend not only on the infarct size but also upon enzyme contributions from inflammatory infiltrates in the heart. Patients in shock without myocardial infarction show no appreciable elevation of MB isoenzyme CPK. Over 75 percent of CPK activity loss occurs in 24 hours from the time of necrosis, indicating that CPK is a most specific and expeditious indicator of irreversible myocardial damage.[46-49]

Although serial CPK determination promises to be a valuable method in determining infarct size, it still may not predict development of cardiogenic shock, since shock may develop fairly early before a complete CPK profile is developed, and also because prior infarcts are not considered in the calculation.

Other studies using radioisotope localization in the heart show promise in noninvasive quantification of infarction.[50]

HEMODYNAMIC CONSIDERATIONS: MYOCARDIAL INFARCTION

In cardiogenic shock hemodyamic abnormalities are usually more pronounced than in uncomplicated myocardial infarction. Knowledge of the causes of such abnormalities in myocardial infarction leads

to a better understanding of the more severe shock syndrome. Myocardial infarction is characterized by the following sequence: (1) initial insult to the myocardium (developing infarct) with a bordering ischemic area; (2) compliance and contractility changes in the left ventricle; (3) abnormalities in forward flow (cardiac output) with adverse consequences to the peripheral vasculature and organ metabolism; and (4) abnormalities in back pressure to the pulmonary circulation and right heart.[51-53]

Compliance and Left Ventricular Filling Pressure

Myocardial infarction produces changes in both compliance and contractility of the left ventricle. The left ventricular end-diastolic pressure (LVEDP) is determined in part by compliance changes. Compliance is a measure of the ability of the left ventricle to accept volume loads with little change in pressure.[54-57] In experimental myocardial infarction, diastolic volume may be similar to control values, but with elevated end-diastolic pressure.[55] This may be the result of increased stiffness in the infarcted area due to edema, necrosis, and infiltration by inflammatory cells. Increasing stiffness may be beneficial by decreasing the typical aneurysmal bulging of the left ventricle which occurs immediately after initial ischemia, and which is associated with reduction in effective stroke volume due to the bulging.[54-55]

Compliance is a general term relating left ventricular filling pressure with volume changes. There are several indices of compliance abnormality.[55-57] A purchase of compliance may be gained by measuring LVEDP, subtracting end-systolic pressure, and dividing by stroke volume (See Appendix).[55] Although decreased compliance can be associated with increases in end-diastolic pressure after a myocardial infarction, left ventricular peak systolic dp/dt, stroke work and cardiac output may remain normal (See Appendix). Thus, LVEDP is not necessarily affected by changes in the contractile state after myocardial infarction.[55] Conversely, congestive heart failure may result from compliance abnormalities without severe dysfunction of contractility (Fig. 1).

Contractility and Active Stiffness

In contrast to compliance, which relates to diastolic filling of the ventricle, contractility involves systolic events. Left ventricular systole is dependent upon contractility and "active stiffness," the latter relating to the inertia which prevents the left ventricle from contracting.[58] Contractility may be measured *in vivo* using a catheter-tip transducer allowing a high fidelity recording of pressure developed by the ventricle in early systole. A high speed recording is used to relate developed left ventricular pressure to instantaneous pressure during isovolumic contraction of the ventricle. This allows a purchase on the velocity of contractile element shortening (V_{CE}) which in turn provides a measure of force-velocity relations in the ventricle. A recent study suggests that determination of contractility has little prognostic significance in myocardial infarction, there being a large overlap in values in survivors and non-survivors.[59]

Active stiffness refers to overall stiffness of the contracting ventricle. In experimental animals, active stiffness does not appear to change in the early infarct period but may decrease chronically, in part because of the development of thin aneurysmal tissue in the initial infarct site, which is more elastic than the muscle it replaces. Decrease in active stiffness may decrease efficiency of ejection, because work is diverted by decreased active stiffness from fiber shortening to force generation, which requires increased oxygen consumption.[58]

Cardiac Work and Development of Tension

The cardiac workload is exceedingly important in acute myocardial infarction because oxygen need is proportional to cardiac work, and such work might act adversely in ischemic areas bordering the infarct site, leading to extension of the in-

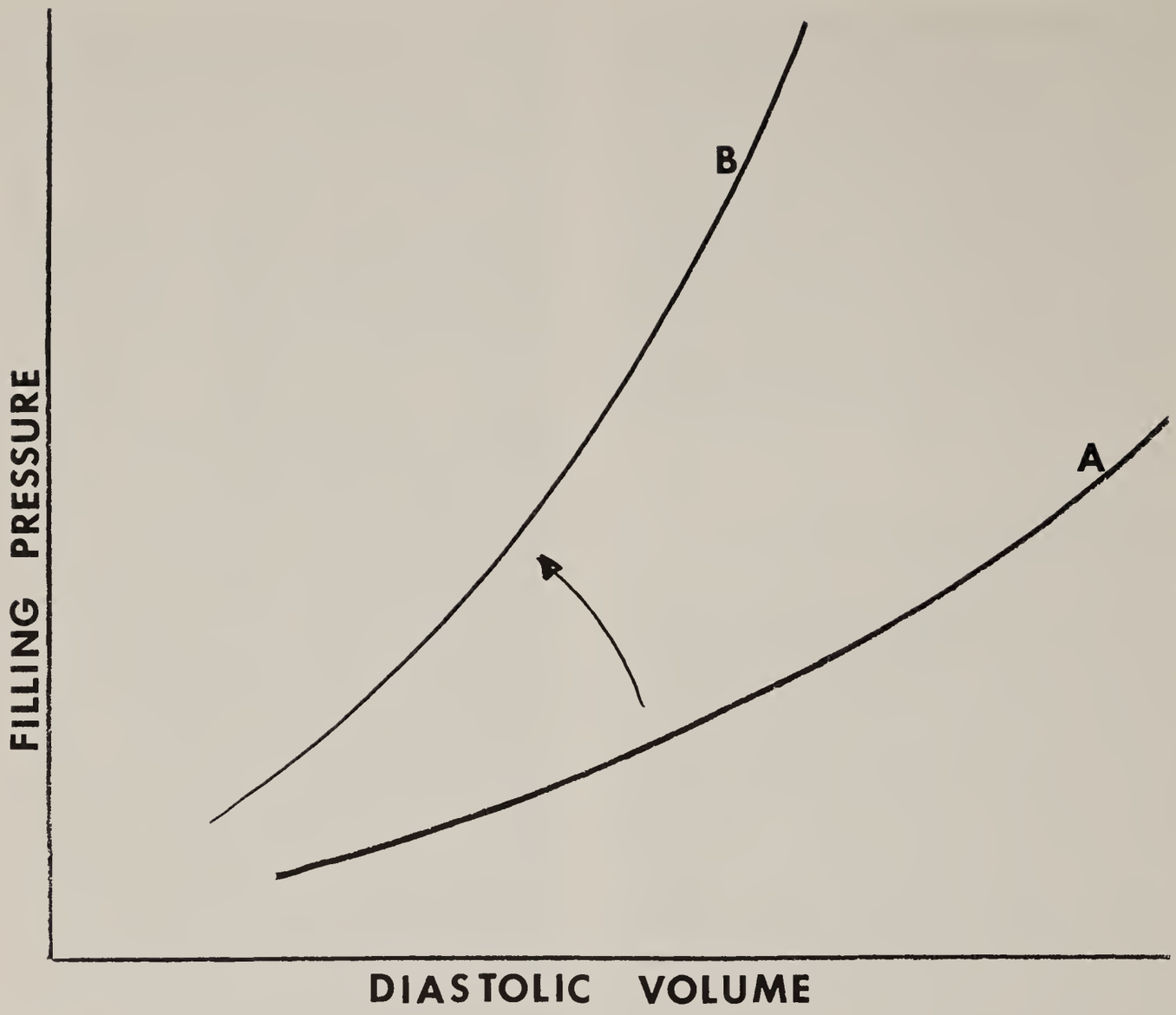

Fig. 1—Effect of decreased compliance on left ventricular (LV) filling pressure. As compliance decreases (from A to B), the filling pressure increases for a specific diastolic volume. In myocardial infarction, the decreased compliance tends to produce increased LV filling pressure and prevent increased end-diastolic volume. The result is an increased pulmonary capillary wedge pressure.

farct. A criterion for increased oxygen consumption is the peak tension developed in each section of myocardium. The increase in chamber pressure of the left ventricle is related to the wall tension by the equation: $P=2HT/R$, where P=chamber pressure, R=radius of LV chamber, T=myocardial wall tension, and H=LV wall thickness.[60]

Thus, to generate a specific left ventricular chamber pressure, decreasing the left ventricular end-diastolic volume would result in decreased peak systolic tension. Put in another way, with a larger end-diastolic volume, it would require a greater development of peak tension to produce a given systolic chamber pressure. An increasingly thick ventricular wall would permit build-up of intracavitary pressures with less peak tension. The corollary to this is that more oxygen would be required by the myocardium with increased end-diastolic volume or decreased wall thickness to reach a given systolic chamber pressure.

Abnormalities of Cardiac Output and Consequences: Early Myocardial Infarction

In the presence of focal myocardial damage, stroke volume may be decreased due to abnormalities of contractility.[59,61-63] Stroke volume may be maintained by ventricular dilatation, associated with increased fiber shortening of the non-infarcted left ventricular muscle. On the other hand, decreased compliance might

reduce left ventricular end-diastolic volume. Experimental studies show that in the immediate infarct period, end-diastolic volume usually is not increased.[61] LVEDP is related to compliance changes, as we have discussed. In normal man, large increases in stroke work may be associated with minimum increases in LVEDP, but in patients with left ventricular compliance abnormalities, small changes in stroke work may occur only with large increases in LVEDP with ensuing pulmonary congestion.[62]

In early myocardial infarction, hemodynamic changes usually consist of increase in peripheral resistance, reduction in stroke volume, and variable decreases in blood volume.[63] On the other hand, widely differing changes in peripheral resistance may occur.[64] Low peripheral resistance may result from impulses initiated in the heart, producing a vagal and hypotensive effect.[64,65] In this situation, stroke volume may actually increase. In experimental animals with coronary occlusion, a reflex decrease in sympathetic stimulation of the peripheral circulation has been found, possibly due to reflexes from ventricular stretch receptors.[66]

HEMODYNAMICS IN CARDIOGENIC SHOCK

Cardiogenic shock resulting from myocardial infarction is invariably associated with low cardiac output, resulting in decreased urinary output, decreased mentation, cool and clammy extremities due to sympathetic effects, and a decreased aortic systolic pressure, usually below 90 mm Hg.[4] Shock may be associated with hypovolemia, in which case the LVEDP and mean pulmonary capillary wedge pressure (PCWP) may be relatively low(less than 15 mm Hg.) When shock is secondary to extensive myocardial damage alone, PCWP is usually elevated. Occasionally, in this situation, the PCWP is low but usually increases markedly after a fluid load, if hypovolemia is not present. Mortality after shock due to pump failure from extensive myocardial injury is 80 to 90 percent.[4]

Hypovolemia has been shown to occur with cardiogenic shock after experimental myocardial infarction. This usually follows the development of shock.[13,14] Peripheral vascular resistance may be variable, although it usually increases.[59,67] Decreased peripheral vascular resistance after myocardial infarction with or without shock may be 1) increased left-sided stretch or pressure, 2) myocardial anoxia which may reflexly lower systemic vascular resistance and venous tone.[59] Decreased peripheral vascular resistance with constant stroke volume may in turn lower mean aortic pressure to a level near the critical closing pressure of the coronary arteries (30 mm Hg) when the peak arterial pressure is 60 to 70 mm Hg, as frequently occurs in cardiogenic shock.[59,68]

Shock after myocardial infarction is frequently associated with decrease of cardiac output as much as 50 percent of normal.[28] Stroke volume may be as small as 33 percent of normal. Central blood volume is not increased in cardiogenic shock, possibly due to increased capacity of the peripheral venous system.[28] Other possible causes of hypovolemia include inadequate fluid intake, excessive loss of fluids, and loss of intravascular volume with acidosis and unrecognized gastrointestinal hemorrhage.[69] In advanced stages of perfusion failure, severe constriction of the distal arteries may account for large pressure gradients between the root of the aorta and these arteries (sometimes in excess of 30 mm Hg).[28] Thus, indirect peripheral systemic pressure recordings may inaccurately reflect aortic root perfusion pressure.

Little change occurs in cardiac index with changes in the atrial contribution to ventricular filling during cardiogenic shock.[70]

Although in some experimental shock studies, high peripheral pressure is associated with poor prognosis,[71] in clinical situations, systemic vascular resistance appears similar in shock and non-shock groups.[4,72]

Pulmonary Artery and Pulmonary Capillary Wedge Pressure Monitoring in Cardiogenic Shock

Central venous monitoring, *i.e.*, recording pressure from the right atrium or great veins does not necessarily reflect left ventricular diastolic pressure changes (Fig. 2).[73] This is crucial, since increases in left ventricular filling pressure can lead to increased pulmonary capillary pressure and hence pulmonary edema. Thus, in measuring the effects of a fluid load, especially in the case of acute myocardial infarction, it is important to have a purchase on left heart chamber pressures.

As we have noted before, left ventricular compliance affects left ventricular filling pressure, as does absolute ventricular volume.[55-57] In myocardial infarction, left atrial mean pressure correlates poorly with left ventricular end-diastolic volume, indicating the importance of compliance changes in relation to pressure abnormalities of the left side of the heart. The sharp increase in left ventricular pressure following atrial contraction therefore contributes little to mean atrial and pulmonary capillary pressures.[51,74] Since LVEDP may be markedly higher than left ventricular pressure before atrial contraction, mean left atrial pressure may be a better estimate of fluid needs than LVEDP (Fig. 3).[51]

One clinical study showed good corre-

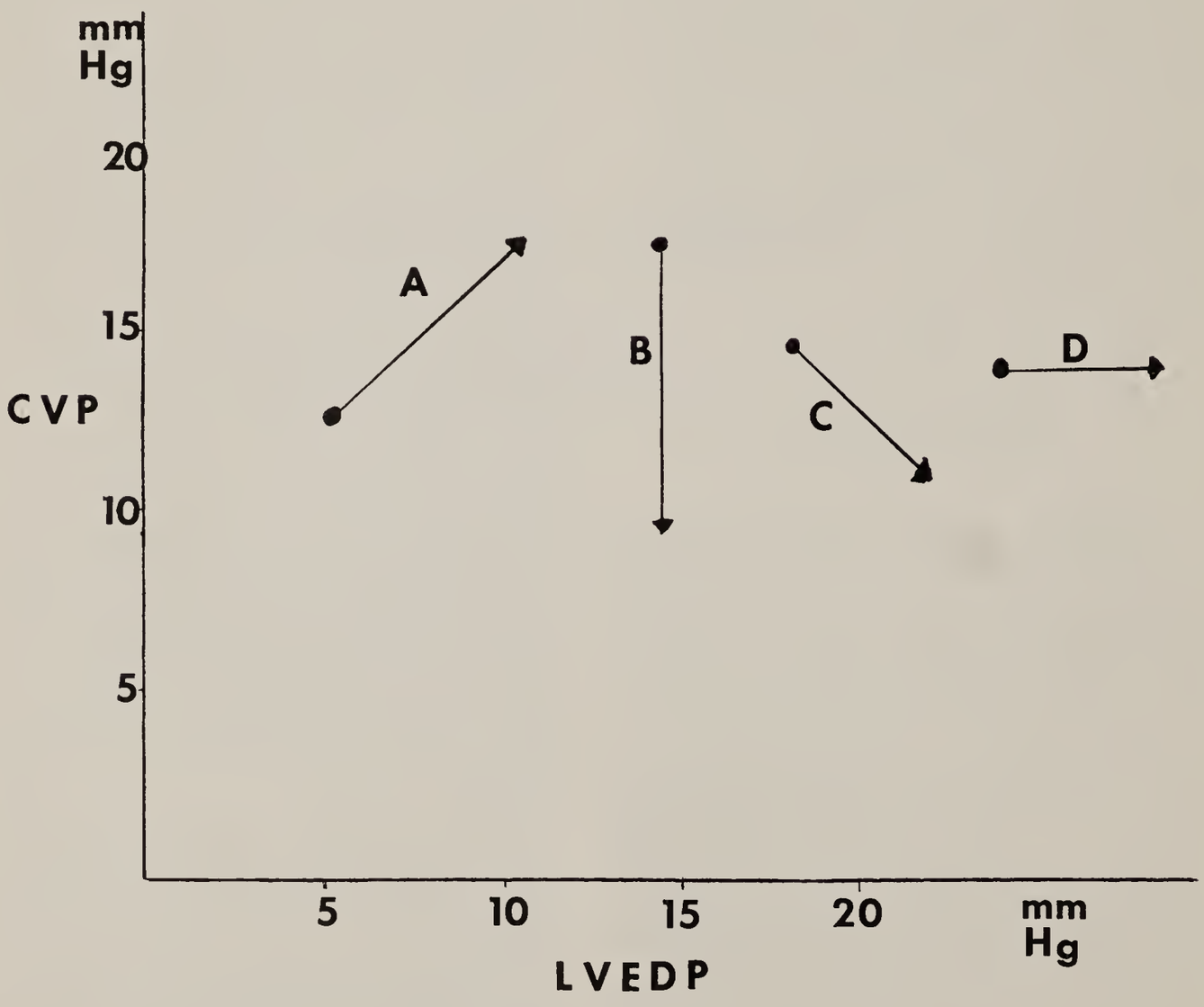

Fig. 2—Demonstration of poor correlation between changes in left ventricular end-diastolic pressure (LVEDP) and central venous pressure (CVP), especially in acute myocardial infarction and in patients receiving pressor agents. In A, CVP and LVEDP both increase. In B, LVEDP decreases with no change in CVP. In C, CVP decreases while LVEDP increases. In D, CVP is unchanged while LVEDP increases (Modified from Gunnar and Loeb—Reference 109).

lation in myocardial infarction shock between pulmonary artery end-diastolic pressure (PAEDP) and LVEDP, or PAEDP and left ventricular pressure before atrial contraction.[75] There were no changes in correlation with oxygen breathing, or use of inotropic agents. It was found that a PAEDP greater than 15 mm Hg was nearly always associated with elevated LVEDP. PAEDP may also be related to catheter position. In patients with mechanical respirators, PAEDP may be higher than LVEDP because the thick left ventricular wall is less affected by changes in intrathoracic pressure. In 50 percent of the studies, PAEDP exceeded LVEDP, and in 28 percent LVEDP exceeded PAEDP.[75] Another study showed good correlation between PAEDP with pulmonary artery wedge pressure but not LVEDP.[76] With superimposed pulmonary vascular disease, PAEDP may be markedly higher than LVEDP. Thus, although PAEDP may give some purchase on left-sided events, it is not an accurate reflector of left ventricular changes.

PCWP is the most accurate reflector of mean left atrial pressure and the need for fluid replacement. Until recently, this measurement could not be readily made at the bedside; but, with the development of a balloon-tipped catheter which can be inserted through a peripheral vein, this measurement may now be obtained routinely with a minimum of morbidity.[77] The catheter is advanced into one of the main pulmonary arteries, and the balloon is inflated for 10 to 15 seconds, preventing forward flow temporarily and allowing effective purchase of pulmonary capillary pressure without advancing the catheter into a wedge position (Fig. 4).

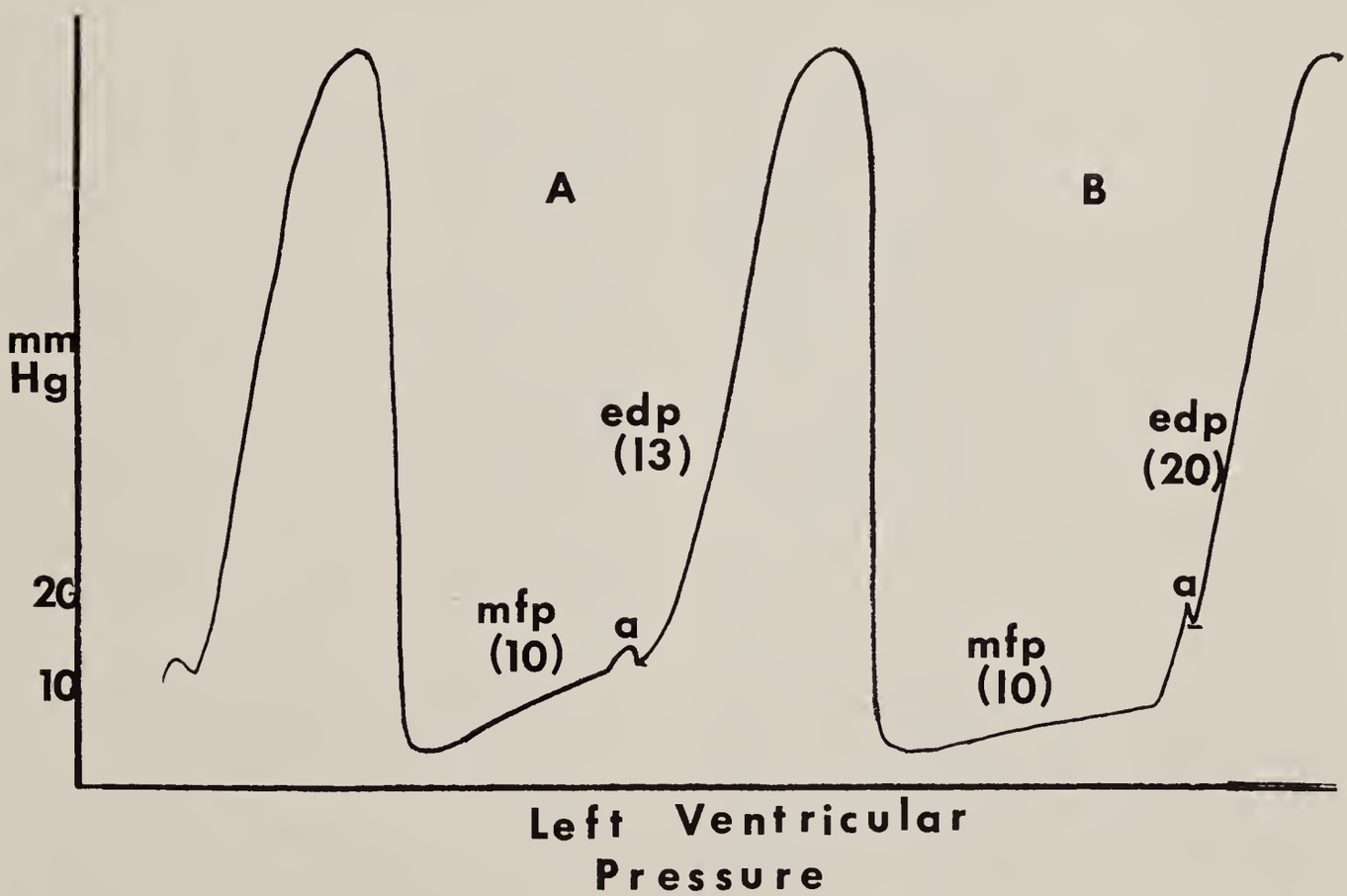

Fig. 3—Left ventricular (LV) end-diastolic pressure and mean left ventricular filling pressure variations. A=a wave (contribution of atrial contraction to left ventricular pressure). Although the LV end-diastolic pressure is higher in B than A, filling pressure before the a wave is lower in B than A. The resultant mean filling pressure (end-systole to end-diastole) in both is 10 mm Hg. It is the mean filling pressure which largely determines pulmonary capillary wedge pressure, not the LV end-diastolic pressure.

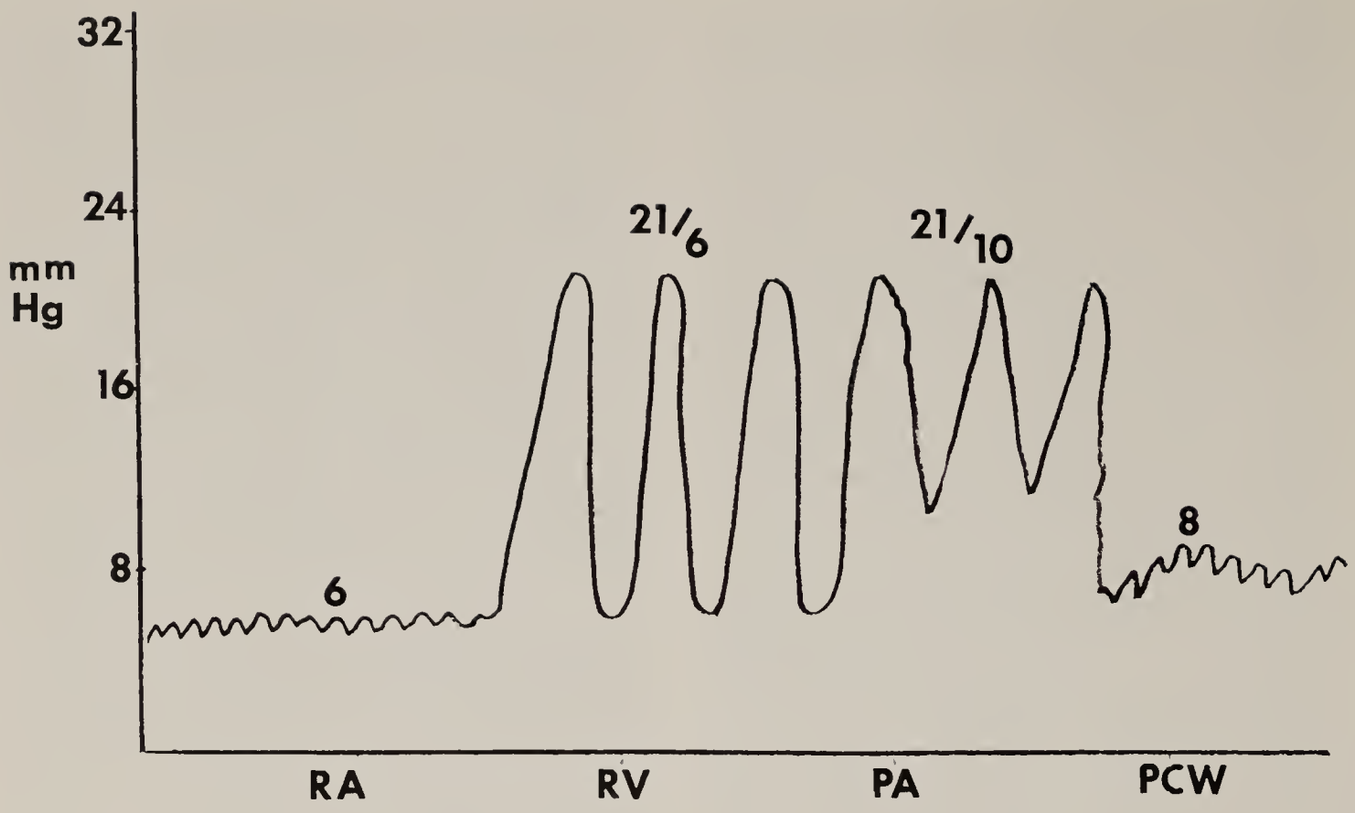

Fig. 4—Changes in pressure trace which determine location of catheter tip. RA=right atrium. RV=right ventricle. PA=pulmonary artery. PCW=pulmonary capillary wedge. With a balloon-tipped catheter, the PCW pressure is obtained by inflating the balloon while the catheter tip is in the pulmonary artery.

PROGNOSTIC INDICES IN CARDIOGENIC SHOCK

Since the development of cardiogenic shock *per se* is associated with high mortality, efforts have been made to relate hemodynamic parameters with prediction of death and possibly to predict the development of shock. Indicators of 100 percent mortality in cardiogenic shock in one study included (1) PAEDP or LVEDP greater than 28 mm Hg, or (2) PAEDP or LVEDP greater than 15 mm Hg with cardiac index less than 2.3 L/Min/M^2 in 75 percent.[78] One subgroup with low LVEDP improved with rapid infusion of dextran or dextrose/water, with proportionately greater increases of cardiac index than LVEDP. Those responding had PAEDP or LVEDP of 20 mm Hg, or less, before fluid loading.

Other studies have shown similar good response with shock associated with initially low pressures.[69] Prognosis after myocardial infarction has been related to central venous pressure, A-V 0_2 content difference, and cardiac index.[79] Others have correlated mortality with low left ventricular stroke work index, low cardiac work index, or high peripheral vascular resistance.[51,80,80a]

Since many of the studies were performed on patients already in cardiogenic shock, poor prognosis would be expected in the majority. However, there are instances where patients not in direct shock may exhibit poor hemodynamic function, and it is in this group that early interventions, *e.g.*, intra-aortic balloon assist, may prevent the development of shock.

CORONARY ARTERY BLOOD FLOW AND MYOCARDIAL METABOLISM

Coronary artery blood flow in cardiogenic shock generally correlates with mean aortic pressure. The flow-pressure curve is linear about 70 mm Hg, and flow decreases markedly below this pressure, with no flow at 30 mm Hg pressure.[81] Increased coronary flow is associated with increased extraction of oxygen and lactate. When coronary flow is decreased, oxygen

consumption is decreased. Oxygen content of coronary venous blood does not necessarily decline.[28]

When oxygen tension falls below a certain level, mitochondrial ATP synthesis is retarded and anaerobic glycolysis in cytoplasm becomes predominant. Lack of oxygen blocks oxidative phosphorylation with fall in cellular creatine phosphate, ATP and glycogen. Increase in phosphate, AMP, lactate, hydrogen and neutral lipids occurs and the cell gains water. Lysosomal particles rupture and enzyme systems fail. An increase in hydrogen ion concentration may depress myocardial force and depress responsiveness of cardiac contractile proteins to calcium ions.[43,82-88]

Although at low levels of coronary flow, increasing coronary flow up to a certain point will increase myocardial oxygen consumption,[81,89,90] under the usual circumstances of coronary flow, oxygen consumption of the myocardium will increase with increased peak-developed tension of the left ventricle and increased maximum velocity of contractile element shortening (VMAX).[89] Simultaneously, opposite changes in tension and contractility could cancel out changes in myocardial oxygen consumption. Over 90 percent of myocardial oxygen consumption is determined at the time peak tension is reached. Contraction of the myocardium consists of two phases: (1) isometric contraction—stretching of the series elastic elements and contraction of the contractile elements, producing tension without fiber shortening; (2) isotonic contraction—physical shortening of the myocardial fibers. The energy cost of isometric contraction is far greater than that of isotonic contraction. Thus, oxygen consumption is greater with pressure work than with flow work, or with increase in heart rate.[89-91]

Although anoxic solutions infused into the coronary artery will markedly decrease contractile force development of the myocardium, the fall is even greater without perfusion.[92] It is possible that continued flow in oxygen-deficient systems might allow disposal of waste metabolites and prevent alterations in electrolyte distribution across the cell membrane. Thus, we must differentiate two factors involved in decreased function of the myocardium: (1) Hypoxia = decrease of oxygen available to the cell; and (2) ischemia = decrease in coronary blood flow available regardless of oxygen content.

In cardiogenic shock, as well as other states of myocardial ischemia, the arterioles supplying the occluding arteries are maximally dilated.[93,94] Post-occlusion perfusion is dependent upon mean aortic pressure and not upon further dilatation of the arterioles, although the large arteries proximal to the occlusion may be still capable of dilatation.[95]

Inotropic agents which have coronary vasoactive effects can be used to compare the responsiveness of the normal and diseased coronary vascular bed. Isoproterenol can increase myocardial blood flow by almost 100 percent in normal subjects.[96] With coronary artery disease, total coronary flow can be increased almost as much. In diseased coronary arteries with intracoronary (bridge) collaterals, increase in flow may be demonstrated with isoproterenol. Flow does not increase as much in post-obstructed vessels supplied by intercoronary collaterals.[96] Thus, intercoronary collaterals may contribute insignificantly to coronary flow reserve.

Although inotropic agents such as isoproterenol may increase coronary total flow in situations of ischemia or necrosis flow may be increased to the normal myocardium at the expense of the ischemic myocardium, resulting in a "coronary steal."[97]

Studies of extent of infarction by mapping ST segment elevation from many areas of the anterior chest show that an increase in severity and extent can occur with isoproterenol, ouabain, glucagon, bretylium or tachycardia, and decrease may occur with propranolol.[48] Variations in ST segment elevations may occur when drugs are given for as long as three hours after experimental coronary occlusion. ST segment elevation correlates well with decreased myocardial oxygen availability and the development of anerobic metab-

olism in the segments of myocardium involved with ischemia. ST segment elevation may also be caused by stimulation of areas within the central nervous system and stellate ganglia and changes in the ionic milieu of the myocardium.

It should be stressed that, in accounting for low arterial oxygen tension (pO_2), increased pulmonary shunting occurs in myocardial infarction, and more so with the development of cardiogenic shock.[98-102] The low pO_2 may lead to increased arrhythmias, especially in patients who are receiving digitalis preparations.[103]

In summary, myocardial ischemia is usually due to decreased pO_2 associated with low coronary flow. In areas of ischemia, oxygen delivery to the myocardium can be increased only by increasing the mean aortic pressure, since the vessels to the area are already maximally dilated. Inotropic agents given in situations of myocardial ischemia may increase total coronary flow, but at the expense of regional flow to the ischemia area. Oxygen requirements of the myocardium depend mainly upon the early systolic pressure events. Thus, decreasing developed tension in the myocardial wall may greatly decrease the need for oxygen and make the balance more favorable for viability of ischemic myocardium.

THERAPY OF CARDIOGENIC SHOCK

Reversal of cardiogenic shock after myocardial infarction is as yet an unrewarding task, but efforts to accomplish this have produced much information about myocardial infarction, pharmacodynamics, and the development of simple yet reliable counterpulsation devices.

The current therapy of cardiogenic shock involves a more aggressive approach than previously, because of the high mortality found even with various pharmacologic interventions. A rational approach to treating the development of shock is an adequate hemodynamic evaluation of the syndrome. In order to accomplish this, two bedside procedures may be employed. (1) Percutaneous arterial catheterization will allow a continuous recording of central arterial pressure. (2) Insertion of a balloon-tip catheter from a peripheral vein into the pulmonary artery will afford periodic evaluation of the mean PCWP, which reflects the mean left atrial pressure. Low wedge pressure in the face of a shock syndrome suggests hypovolemia, and attempts should be made to correct this. If hypovolemia is not present, or if PCWP rises markedly with a fluid load, true pump failure of the left ventricle has occurred. In such a situation the prognosis is dismal without further therapy.

Over the past 20 years, treatment has progressed from the use of inotropic agents, to counterpulsation, to the combination of counterpulsation with emergency coronary bypass surgery. The main precepts of therapy are (1) to decrease the work of the heart, (2) to increase coronary arterial flow, and (3) to maintain or increase cardiac output. These aims have been successfully accomplished at the bedside using counterpulsation, most commonly by intra-aortic diastolic phase shift balloon catheters. They have been quite effective in temporarily improving the hemodynamic and metabolic abnormalities, but eventual hospital mortality has not significantly decreased using only this technique.

INCREASE IN CORONARY ARTERY PERFUSION

Decreased coronary perfusion pressure causes subendocardial underperfusion.[104] Agents with such diverse properties as dipyridamole, norepinephrine and propanolol have been shown to increase blood flow to the left ventricular subendocardium of normotensive and hypertensive animals with myocardial ischemia. Other studies have shown that hypotension is associated with decreased flow in both the anterograde and collateral coronary circulation but that a slight rise in systemic pressure (20 mm Hg) in hypotensive animals can often increase coronary flow by 30 percent.[105] Increase in perfusion pressure by modest amounts may therefore produce considerable effects upon coro-

nary flow, and this became the rationale for using pressor agents in cardiogenic shock after myocardial infarction.

EARLY STUDIES OF PRESSOR RESPONSE

An early review of myocardial infarction shock by Binder, et al questioned the efficacy of therapy without strict criteria for defining the syndrome.[106] They found that when shock was defined as low systolic pressure, clinical signs of peripheral circulatory collapse, and absence of life-threatening arrhythmia or complicating conditions not attributable to myocardial pump failure, non-specific therapy (morphine and oxygen) produced a pressor effect in 23 percent of patients, but the ultimate mortality was 82 percent. Transfusion had no effect on mortality, and although levarterenol produced a pressor effect in almost all patients, ultimate mortality was 68 percent. Review of the literature to 1954 by these authors had already demonstrated that transfusions did not decrease mortality, and that levarterenol was associated with an average mortality of 58 percent.[106] Although the latter mortality figure for shock after myocardial infarction is now considered quite low, there were wide variations in mortality figures in the earlier studies using pressor agents. This was due to (1) non-uniform criteria, (2) variation in duration of shock before therapy was started, and (3) numerically small series. In this review it was also found that digitalis did not increase the pressor effect of levarterenol in the absence of heart failure.[106]

Another early study of a large group of patients with cardiogenic shock demonstrated that shock mortality was markedly lower in a substantial subgroup responding within three hours to "routine" measures without the use of pressor agents.[107] Therapy included the use of anti-arrhythmic agents, digitalis and fluids for complications of arrhythmias, hypovolemia and congestive failure associated with the shock. Almost 90 percent of these responders survived hospitalization. Others, not responsive to routine measures, were given pressor drugs, and although a pressor response was seen in many, mortality remained approximately the same as in a previous control group (80 percent). Steroids in moderate doses (150 to 200 mgm cortisone, daily) were not effective in producing a pressor response.[107]

Thus, these early studies demonstrated that reversal of the shock syndrome frequently was effected by treating specific complications which might cause hypotension, such as hypovolemia and arrhythmias. If shock was associated with myocardial damage alone, without these superimposed conditions, mortality remained high, despite treatment.

PLASMA VOLUME EXPANSION

In the patients with cardiogenic shock associated with low left ventricular filling pressure, the syndrome is often reversed by initiation of a fluid load, either 5 percent dextrose/water or low molecular weight dextran. Dextrose/water may be given at 20 ml/min for 10 to 15 minutes, with central venous or pulmonary capillary wedge pressure measured every three minutes. A pressure rise of more than 3 cm water (central venous pressure) or 2 to 3 mm Hg (pulmonary capillary wedge pressure) would be reason for terminating the infusion.[108–111] Similarly, dextran can be infused at 5 to 10 ml/min up to 500 ml, with central venous or pulmonary capillary wedge pressure checked after each 100 ml infused.[69,108,110] Low molecular weight dextran reduces sludging of red cells and improves flow rates, but may produce renal toxicity.[108]

In the event that pulmonary capillary wedge pressure cannot be monitored at the bedside, a central venous (right atrial) pressure may afford some estimate of rise of left heart pressure, since both tend to rise proportionately with fluid infusions.[109,110] It must be stressed that central venous pressure correlates poorly with left ventricular end-diastolic pressure in absolute values (Fig. 2).[109–112]

Plotting left ventricular stroke work index (See Appendix) against left ventricu-

lar end-diastolic pressure or pulmonary capillary wedge pressure may be of considerable value, in assessing improvement of left ventricular function by means of a fluid load.[113] If the curve moves upward and to the right, it suggests improvement. If it moves downward and to the left after a fluid load, the LV may be operating at the peak of its function curve, and improvement with a fluid load is unlikely.

CATECHOLAMINES

Extensive use of levarterenol (norepinephrine), isoproterenol, metaraminol and, more recently, dopamine in cardiogenic shock after myocardial infarction has failed to demonstrate significant decrease in mortality in patients who are unresponsive to volume loading, although transient pressor effects have been noted in many cases.

Norepinephrine has both alpha and beta adrenergic properties. Use of this agent has not increased survival above 30 percent in cardiogenic shock.[109] At small infusion rates, it may increase cardiac output with little effect on peripheral vascular resistance.[116] Although peripheral vasoconstriction can be blocked with phentolamine and chlorpromazine, there is little objective evidence that such drug combinations will produce better effects than norepinephrine alone in myocardial infarction shock.[108]

The state of cardiac output and peripheral vascular resistance may affect the response to norepinephrine. If the cardiac output is initially low with peripheral vascular resistance elevated, norepinephrine increases cardiac output with little change in resistance. With normal or low peripheral resistance and reduced cardiac output, norepinephrine may decrease cardiac output and increase resistance.[117] The effect of pressor amines on peripheral vascular resistance may be modified by (1) acidosis, (2) fatigue produced by excess stimulation, or (3) stronger stimulation by endogenous catecholamines. The latter two possible explanations have little evidence to support them.[117] Metaraminol produces peripheral effects similar to that of norepinephrine but is less potent. Part of its effect is due to stimulation of endogenous catecholamine and there is frequent development of drug tolerance after long infusion of metaraminol.

Isoproterenol has pure beta adrenergic stimulating properties and therefore does not increase peripheral resistance in the renal, mesenteric and musculoskeletal beds as does norepinephrine.[118] Like norepinephrine, at lower infusion dosage, the cardiac effects of isoproterenol may predominate over peripheral effects.[118,119] Thus, infusion rates of 1 to 3 *ug*/min were shown to produce mostly increased chronotropic and inotropic effects while larger infusion rates produced a significant vasodilator effect.[118] In higher doses, reduced perfusion pressure occurs due to peripheral vasodilatation.

Experimental and clinical studies indicate that in cardiogenic shock, norepinephrine appears to have a more pronounced effect on increasing perfusion pressure than isoproterenol.[120,121] Although it may be postulated that isoproterenol has advantages over norepinephrine in not causing renal artery vasoconstriction recent studies indicate that isoproterenol increases renal flow only when administered directly into the renal artery.[122]

The objects of treatment in cardiogenic shock not only sustain cardiac output but also maintain coronary flow, or better, afford an increased coronary flow with reduced left ventricular work. Increases in heart rate, more likely to be produced by isoproterenol, would tend to increase cardiac work. Although some studies indicate an increase in peripheral perfusion with isoproterenol compared with norepinephrine in experimental cardiogenic shock,[112] this advantage is outweighed by the adverse effects of isoproterenol on myocardial metabolism.

Kuhn *et al.*, in studies of experimental myocardial infarction shock, demonstrated an initial increase in coronary flow and oxygen consumption with isoproterenol infusion; after one hour, coronary flow descended to control levels and lactate production of the left ventricle increased

further.[123] Other studies have indicated an increase in myocardial lactate production with isoproterenol, not found with norepinephrine.[3,109,124] Contrary to most authors, Cronin found that lactate production was increased with norepinephrine but not isoproterenol, although coronary blood flow and myocardial oxygen consumption were increased by each agent.[121]

Increased anaerobic metabolism may be noted with isoproterenol despite increased coronary blood flow because of diversion of blood from ischemic areas, to areas supplied by normal coronary arteries.[97,109] The increase in contractile force of the myocardium with decreased arterial perfusion pressure has been noted in animals.[125] In experimental myocardial infarction, isoproterenol caused an increase in left ventricular function, as measured by left ventricular dp/dt and cardiac index; this enhancement was markedly less when infarction involved more than 20 percent of the myocardium.[126] Thus, in situations where cardiogenic shock supervenes, and where probably over 30 percent of the left ventricle is involved by ischemia or infarction, the enhancement of cardiac function might be minimal with an associated decrease in perfusion of ischemic areas.

The lactate production in myocardium found with isoproterenol administration is probably associated with increased anaerobic metabolism because of inadequate oxygen supply. Catecholamine infusion stimulates glycolysis and metabolism of fatty acids, and increased pyruvate produced by glycolysis might compete with fatty acid 2 carbon fragments for entrance into the Kreb's cycle. This could lead to increased production of lactate in the absence of increased ischemia.[124] However, myocardial respiratory quotient does not change after isoproterenol in cardiogenic shok, indicating the pattern of metabolism is not altered.[124] Also, isoproterenol has been found not to simulate lactate production normally, or in non-cardiogenic shock.[124,127,128] Therefore, low supply of oxygen is probably the mechanism of the lactate production produced by isoproterenol in cardiogenic shock after myocardial infarction.

Histochemical studies have shown that catecholamines produce effects similar to ischemic changes of myocardium.[129] Isoproterenol administered subcutaneously in the rat produces gross and microscopic myocardial necrosis, with a close correlation between the dose and extent of necrosis.[130] Isoproterenol produces thickening and swelling of mitochondria, with swelling of the endoplasmic reticulum.[131,132] Hence, hemodynamic, metabolic and pathologic studies indicate that isoproterenol may have considerable adverse effects on the myocardium, especially under the circumstances of severe ischemia.

Prevailing opinion is that isoproterenol should be used cautiously, if at all, in patients with myocardial infarction with cardiogenic shock. The drug agent may be of some use in severe mitral insufficiency associated with infarction, by preventing increase in peripheral vascular resistance which would enhance regurgitant flow.[109] Its use may cause adverse effects such as (1) arrhythmias and (2) marked decrease in peripheral vascular resistance with ensuing hypotension.[110] Norepinephrine may be of some use in situations where the aortic pressure must be maintained in the absence of cardiac assist devices.

Dopamine has been studied in recent years in clinical heart failure including cardiogenic shock. It increases coronary, renal and mesenteric blood flow, with associated increases in systemic pressure.[107–109] Increased urinary output has resulted from its use in shock.[133] Its effect on the renal circulation is not a beta-adrenergic property and therefore is not inhibited by beta blockers.[108] Unlike the effect of isoproterenol, tachycardia is not produced, and peripheral resistance is decreased. In cardiogenic shock, dopamine increases cardiac output more than norepinephrine and less than isoproterenol, and increases arterial pressure more than isoproterenol, but less than norepinephrine.[134] There is little indication that it is more effective than the other catecholamine agents in decreasing ultimate mortality from cardiogenic shock.

DIGITALIS

In the absence of congestive heart failure, there appears to be little influence of digitalis upon reversing cardiogenic shock, although it may reduce functional mitral regurgitation.[108] In one study of cardiogenic shock patients, it produced a prompt pressor effect, with increased peripheral vascular resistance.[135] No change in left ventricular end-diastolic pressure was noted. Cardiac output was not increased. The work of the left ventricle increased.[135] Another study demonstrated a reduction in left ventricular end-diastolic pressure with a significant rise in arterial pressure, cardiac output, left ventricular stroke work and peripheral vascular resistance.[136] Digitalis appears to produce toxic arrhythmias even with therapeutic levels during the first 24 hours after infarction, and should therefore be used cautiously in this setting.[103] Most investigators in the field do not consider digitalis useful in cardiogenic shock, except possibly in instances where the left ventricle is moderately dilated.[109,118] In the latter circumstance, decrease in end-diastolic volume produced by digitalis could decrease peak tension of the left ventricle and thus reduce the work of the heart while sustaining cardiac output.

GLUCAGON

Glucagon is a potent inotropic agent which stimulates the adenyl cyclase system to produce cyclic AMP. This resembles the mechanism of catecholamines, but its effects are not blocked by beta-receptor blocking agents. It does not produce the cardiac arrhythmias that catecholamines do.[137-141] In cardiogenic shock, it increases cardiac output and stroke volume.[106] Its disadvantages are an increase in pulmonary vascular resistance and increased left ventricular work.[109,134] Its advantages are increase in cardiac output, urinary output by a direct effect on the renal tubules, and the absence of arrhythmogenic properties.[109,118,134] Its main use has been in congestive heart failure, and there has been no evidence that it greatly reduces survival in the patient with cardiogenic shock after myocardial infarction.

PERIPHERAL VASODILATORS AND STEROIDS

Peripheral vasodilators decrease impedance to left ventricular emptying. Acute administration of such agents as nitroglycerine, nitroprusside or phentolamine decreases left ventricular filling pressure and increases cardiac output. The increase in cardiac output is more likely in patients with initially low outputs, especially in acute myocardial infarction.[143] Nitroprusside in myocardial infarction causes a fall in left ventricular end-diastolic pressure without change in heart rate and slight decrease in mean arterial pressure. In patients with congestive heart failure or cardiogenic shock, the cardiac output may increase.[144] Nitroglycerine and phentolamine may produce a reflex increase in heart rate.[143] Myocardial oxygen consumption increases with phentolamine but usually decreases with nitroprusside and nitroglycerine. Peripheral vasodilators may have their best use in myocardial infarction with markedly increased left ventricular filling pressure. They allow a reduction in preload and afterload of the left ventricle, thus decreasing myocardial oxygen consumption while maintaining or increasing cardiac output and decreasing pulmonary capillary hypertension.[144] Their use in cardiogenic shock may be hazardous because of decreased perfusion pressure of the coronary arteries, but they may be useful as adjuncts to treatment with counterpulsation devices.

Corticosteroids in large doses may be used as peripheral vasodilators, and have been of some use in maintaining peripheral perfusion in non-cardiogenic shock.[118] In experimental studies of cardiogenic shock, methylprednisolone reduced vasoconstriction and increased urinary output.[145] The effect of corticosteroids in reducing mortality after cardiogenic shock after myocardial infarction has not been demonstrated, but they may have an ancillary role in sustaining urinary output and peripheral blood flow in shock syndrome. Recent studies indicate that large-dose corticosteroids may decrease infarct

size by stabilizing myocardial lysosomes.[145a,b,c]

COUNTERPULSATION

The effort to accomplish the goals of simultaneously (1) increasing coronary blood flow, (2) decreasing cardiac work, and (3) maintaining or increasing cardiac output has led to the use of counterpulsation devices.[146–149] This technique is being used in many centers for reversal of the cardiogenic shock syndrome after myocardial infarction. It was originally based upon rapid withdrawal and reinfusion of blood from the circulation to decrease afterload during systole and increase coronary flow during diastole. The withdrawal of blood during early systole and reinfusion during diastole caused problems because of hemolysis and the inertia of the system.[149]

A solution to this problem was accomplished by an intra-aortic balloon catheter, which operated on an impulse triggered by the QRS complex of the patient's electrocardiogram.[150–152] The balloon, located in the descending aorta, is rapidly inflated and deflated with a low density gas (at first carbon dioxide and, presently, helium). The inflation of the balloon during diastole increases aortic diastolic pressure and thus increases perfusion pressure of the coronary arteries. Deflation just before systole reduces impedance to ejection of blood by the left ventricle. The result is augmentation of ventricular performance without changing the intrinsic contractile state of the left ventricle (Fig. 5). The increase in coronary flow during diastole increases oxygen consumption and reverses lactate production by the myocardium.[2,153,154] Effects of increased myocardial oxygen consumption and decreased left ventricular end-diastolic pressure are more pronounced with initially reduced coronary blood flow.[154] A reflex reduction of systemic vascular resistance has been found to occur as well.

Diastolic augmentation has been found

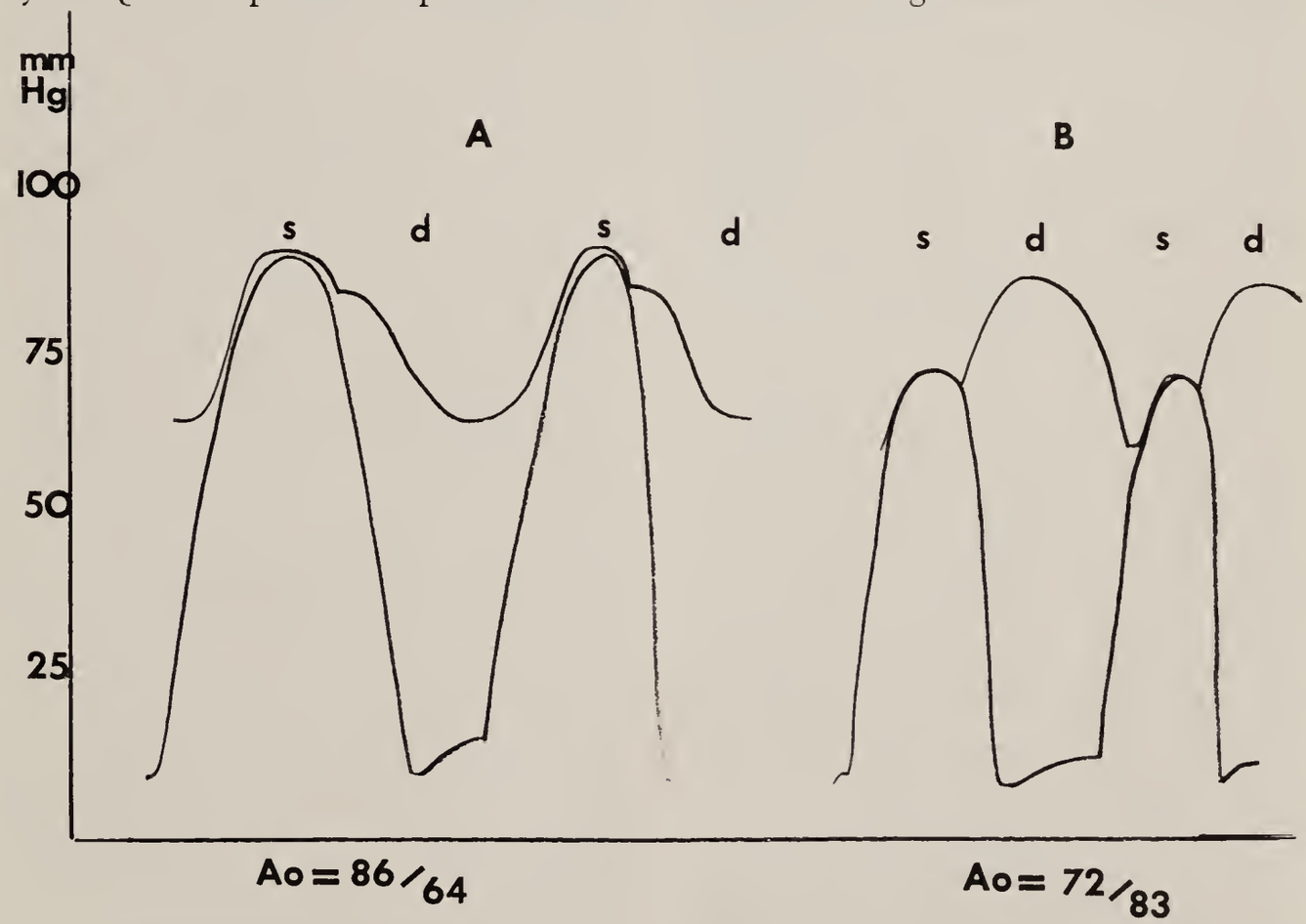

Fig. 5—Demonstration of effects of diastolic counterpulsation on aortic and left ventricular pressure recordings in shock. A=the pressure recording before counterpulsation. B=the recording during counterpulsation. Diastolic augmentation increases diastolic pressure in the aorta, leading to increased coronary artery blood flow. The marked decrease in pressure at the end of diastole due to deflation of the intra-aortic balloon decreases afterload, and the peak systolic pressure is decreased. This reduces the work of the left ventricle. S=systole. D=diastole. Ao= aortic systolic/diastolic pressures.

to decrease expected infarct size after coronary artery ligation.[155-157] Its effect on decreasing ischemic area is noted even with simultaneous isoproterenol administration, demonstrated by decrease in ST segment elevation by precordial mapping.[156] Coronary blood flow has been found to remain elevated even after cessation of diastolic balloon pumping.[157]

Technical problems and complications with the balloon catheter have included: rare balloon bursting, some inertia in balloon inflation and deflation, arterial occlusion in the femoral area where the large catheter is inserted, and clotting at the catheter tip. Use of a teflon sleeve at the insertion site and proper catheter positioning has prevented distal arterial occlusion.[158,159] Clotting has been reduced by the use of heparin, and by minimal inflation and deflation of the balloon when counterpulsation is not being used while the catheter is in place.[160,161] Inertia is decreased further by use of a three-segment balloon rather than a single one, thus decreasing pressure pockets.[158,159] Too abrupt a rise in pressure early in diastole may lead to intramural myocardial hemorrhage.[153] Other disadvantages of balloon counterpulsation are the technical difficulty of catheter insertion with severe aortic or iliac atherosclerosis and its contraindication in aortic aneurysm and aortic regurgitation.

A recent cooperative clinical trial of intra-aortic balloon counterpulsation in cardiogenic shock patients at 10 institutions has demonstrated its positive and negative aspects.[160] Positive aspects included increase in coronary artery flow with decreased myocardial lactate production, prompt increase in urinary output, decrease in cool and clammy skin, acidemia, need for pressor agents, and cardiac arrhythmias. Cardiac output increase averaged 0.5 liters/minute. Negative aspects included lack of long-term survival in 82 percent even though initial favorable response to balloon assist was found in the majority of patients. Fourteen percent of patients developed arterial insufficiency in the leg and six percent sustained left ventricular rupture. It must be concluded that balloon assist alone has little effect upon ultimate mortality.

External counterpulsation devices have been under study for the past five years, using diastolic inflation of cuffs around the lower extremities.[162-167] External assist devices may be of use in transporting patients in cardiogenic shock or severe congestive heart failure after myocardial infarction from one facility to another and, indeed, in all patients with infarction. Although there have been some promising results which suggest significant hemodynamic effects using this technique, further clinical trials must be accomplished to obtain better perspective on its value.

Recently, more aggressive treatment of patients with cardiogenic shock has been initiated combining a brief trial of intra-aortic balloon assist followed by coronary angiography and emergency bypass surgery if the hemodynamic and metabolic state does not improve with discontinuation of assist.[168,169] In a recent study of 80 patients placed on balloon assist, 85 percent did not tolerate withdrawal of the assist.[26] Of 24 patients subsequently undergoing emergency coronary artery bypass, nine were discharged from the hospital (37 percent). Of the entire group of 80 patients, 24 percent survived hospitalization, including 10 of 12 who could become balloon independent after 24 hours. The authors defined balloon dependence after 24 hours as a fall in mean arterial pressure to less than 60 mm Hg, a rise in pulmonary capillary wedge pressure to greater than 20 mm Hg, and a fall in cardiac index to less than 2.0 L/min/M^2 when attempts were made to discontinue balloon assist. These results suggest that emergency bypass surgery may allow salvage in a selected group of patients not improved by balloon assist if these patients have correctable coronary artery lesions.

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APPENDIX

Formulae for Left Ventricular Performance Measurements

1. COMPLIANCE: $\frac{P}{V} = \frac{EDP - ESP}{CO/HR}$ **Reference 55**

   P = pressure (mm Hg) V = stroke volume (ml/beat) CO = cardiac output HR = heart rate

2. STROKE WORK: $\underset{(gm\text{-}m)}{SW} = \frac{(MAP - LVEDP) \times SV \times 13.6}{1000}$ **Reference 22**

   SW = stroke work MAP = mean aortic pressure LVEDP = left ventricular end-diastolic pressure
   SV = stroke volume (CO/HR) Minute Work = stroke work × heart rate

3. Mean dp/dt: $\underset{(mm\ Hg/sec)}{dp/dt} = \frac{\text{arterial diastolic pressure-LVEDP}}{ICT}$ **Reference 59**

   ICT = isovolumic contraction time (time between first high frequency vibration of first heart sound S_1 and beginning of left ventricular ejection)

4. Contractile Element Velocity (V_{CE}): $\underset{(muscle\ lengths/sec)}{V_{CE}} = \frac{dp/dt}{KP}$ **Reference 59**

   K = 32/muscle length P = developed pressure of LV. Instantaneous V_{CE} plotted against specific developed pressures from onset of isovolumic contraction to opening of aortic valve. Curve extrapolated to V_{CE} at 0 pressure (Maximum V_{CE}).

5. Total Peripheral Vascular Resistance (Units): $\frac{MAP - \text{mean right atrial pressure}}{\text{Cardiac Output (L/Min)}}$ **Reference 79**

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CHICAGO AND THE TREATMENT OF ABDOMINAL AORTIC ANEURYSMS

Ormand C. Julian

The privilege of presenting a Bevan lecture before this Society, which I most of all cherish among the surgical societies in which I have been privileged to have a membership, is a distinction which I feel is far beyond anything I deserve. Although in considerable awe of the responsibility entailed, I assure you I have looked forward to this occasion with great pleasure. It is, of course, obvious that in order to qualify for this assignment it was necessary for me to retire and leave Chicago, but I do believe this event is worth the great change in environment, the deprivation of most of my longstanding associations, and the downright loneliness which has sometimes resulted during the last year.

We are honoring the memory of Arthur Dean Bevan who lived from 1861 to 1943 and who played a major role in Chicago medicine and in the history of one of our most prominent Chicago medical colleges. He, along with a number of other great men of his period, is responsible for the national and international stature which historically belongs to Chicago surgery.

Doctor Bevan was born in Chicago, the son of a physician. He took his undergraduate work at the Yale Scientific School but came back to Chicago to Rush Medical College, graduating in 1883. Soon thereafter he became a Professor of Anatomy at Oregon State University but he stayed there only two years, returning to Rush Medical College, Department of Anatomy in 1887. His progressive appointments then were Associate Professor of Surgery, Professor of Surgery and finally, Head of the Department of Surgery at Rush Medical College in 1889, 1902 and 1907. He was Chairman of the Department of Surgery at Presbyterian Hospital concurrently with his Chairmanship at Rush from 1907 until he retired in 1934.

I had particular reason to appreciate the leadership of Doctor Bevan when between 1965 and 1971 as Chairman of the Division of Surgery at Presbyterian-St. Luke's Hospital my administration was strongly supported by the income from the $2½ million of the Bevan Fund which had been donated to the hospital by Doctor Bevan, his family, his many friends and grateful patients. If he had any reason to anticipate this remote benefit of his work, I am sure he would have been most pleased with it because at every point in his career he gave generously of his time to a great variety of committees and commissions, all directed toward improvement of medical education and surgical training. He was Chairman of the Committee on Medical Education of the American Medical Association when in 1904 it recommended the establishment of a permanent Council on Medical Education. Upon its establishment he was named Chairman, working with the Council for some 15 years and therefore having much to do with the standardization of medical education and the elimination of many of its dark areas.

The Arthur Dean Bevan Lecture, presented at the Chicago Surgical Society, October 5, 1973

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My own professional interests and the subject of tonight's lecture have lead me to look for some relationship between Doctor Bevan and Alexis Carrel who, together with Charles Guthrie, was working in the Hull Physiological Laboratory of the University of Chicago during the brief period from about 1904 to 1907, a period which coincided with some of the most active administrative and surgical years of Doctor Bevan. I am sure that Bevan must have been more aware than most, of the pioneer work being produced during this constructive period in the infancy of vascular surgery. It was then that many of today's technical principles were established in this field, and although I would not really wish to have been alive then to witness it at the expense of being dead now, I would like to have had a firsthand feeling for it. It was at this point that there began an advance in vascular surgery—the steps being very far apart at first, but later coming rapidly together and serving to transform impossible human vascular situations into remediable disorders.

The conversion of the impossible to the accepted has occurred under a variety of conditions. Some of the advances in vascular surgery have been thought out carefully in advance, tested on experimental animals, and then carried out in man with varying degrees of confidence. Others have developed at the operating table under the spur of sudden inspiration. Those which have succeeded in the hands of their developers have been passed on to the succeeding generations of trainees who, because no one has ever told them that the procedures are difficult, carry them out with an ease not enjoyed by their teachers.

In spite of the best intentions it has proved impossible to make this paper reflect the development of vascular surgery and particularly the surgery of abdominal aneurysms without injecting a certain amount of personal reference of the "as I remember it" variety. I sincerely hope that you will accept without offense my references to the state of vascular surgery as I saw it during my internship and residency years of 1937 to 1942. At that time rupture of an abdominal aortic aneurysm was considered important largely because of the problems in differential diagnosis from other abdominal catastrophies which might be remediable. Thoracic aneurysms were a novelty and always considered as evidence of lues except in the case of dissecting aneurysm which was usually a phenomenon observed at autopsy. Blood vessels were seldom entered surgically, although trauma to them was commonly surgically repaired, but with indifferent success. In spite of the fact that varicose vein development was well understood on a physiologic basis, truly expert surgical treatment of this condition was supplied by very few surgeons in few centers. Among the best surgeons and among those who really put into practice a sure understanding of the pathogenesis of varicose veins was Geza de Takats. Serving de Takats as an intern in 1937 I saw and learned techniques of varicose vein treatment which had not yet been approached at the University of Chicago and Billings Hospital, where I had been a student. Other common vascular procedures were embolectomy and, above all, lumbar sympathectomy, the mainstay of surgical treatment of arterial insufficiency of the legs. As Doctor de Takats' intern I never really saw a lumbar sympathectomy because the major illumination of the field was the headlight which he wore. Therefore, whenever he invited his assistants to look, he of necessity turned his head and the light away to make room, and the deep incision became totally dark. He did, however, teach us to feel the rubbery chain against the spine and when, much to my pleasure, I was given some of these operations to do, I had no difficulty. Actually, my first experience with sympathectomy had been as a student when I assisted Doctor Lester Dragstedt in a transabdominal bilateral sympathectomy in a young man with severe foot changes of true Buerger's disease. In that operation nobody saw the chain in spite of wide exposure simply because not even Doctor

Dragstedt knew exactly where to look and what to look for. In that case, surprisingly, since no ganglionated material was present in the specimens, one side was indeed sympathectomized, and that foot improved.

We were aware that vascular anastomoses had been done and, also, that a variety of ligation procedures had been attempted, sometimes with apparent success, in cases of aneurysms. However, in the Billings Hospital and St. Luke's environments such essential ingredients as patient material, interest, or technical accomplishment were absent, a situation which existed in all but a few centers in the world.

At the end of World War II the only entirely distinct vascular services in Chicago were those headed by Doctor de Takats, one at St. Luke's Hospital and the other at Hines Veterans' Administration Hospital. I was invited at that time by Doctor Charles Puestow to join Doctor de Takats as a consultant in providing services to the veterans on the Hines vascular ward which consisted of 25 beds. My liking for Docter de Takats, rather than any particular preconceived interest in vascular surgery, lead me to divide my attention between the vascular service at Hines Hospital and a general surgical practice at Chicago Memorial Hospital.

One of the first residents on the services was Doctor William S. Dye who took his residency after his army service in World War II instead of just before, as I had done. Our relationship, which later became the most important of my career, began in an environment at Hines which, in retrospect, was almost weird. Our patient load consisted of patients with venous stasis, varicose veins, thrombophlebitis and thromboembolism, arterial embolism, arteriosclerosis and a group of young male patients with Buerger's disease. The size of this patient load is almost unbelievable in terms of today's incidence. The population on our service was seasonal, and we quickly realized that the patients were simply coming into the hospital during the winter to get off the streets, and leaving when spring was well established. The attraction of the hospital was reinforced by the fact that for several years it was our habit to prescribe an ounce and a half of a very good bourbon before the noon and evening meals for all persons with arterial insufficiency. The workload on the ward decreased very abruptly when this practice was discontinued.

I realize that so far nothing has been said really pertinent to the general topic of development of surgery for abdominal aortic aneurysms. However, on the theory that in any lectureship the participation is 50 percent that of the audience and 50 percent the lecturer I want to assure you that half of us is enjoying itself. I have stressed these recollections to develop the atmosphere existing at this earlier time in which there was virtually no prior individual experience on the part of those who were developing the field locally. At this early time—post World War II—at Hines we did, nonetheless, have an intellectual appreciation of some of the possibilities which existed.

The condition of aneurysm of the aorta had been known in modern terms since the middle of the 16th century. Fallopius, who lived from 1523 to 1562, must be credited with the first combined clinical and pathological description of an abdominal aortic aneurysm. The clinical picture presented would immediately suggest the true diagnosis to any medical student today, but in 1556 Fallopius did not understand the pathology until he had done the autopsy. The first description of a ruptured abdominal aortic aneurysm was by Ballonius some four years later. Aside from the outstanding fact that this aneurysm was accurately diagnosed before death, it is also remarkable that syphilis was suspected during life as its cause. The patient had been given mercury treatment at intervals throughout the last years of his life. This attribution by inference that the aneurysm was caused by syphilis was far ahead of the times, because as late as 1905 there was disagreement as to whether syphilis was ever a primary etiology or only a secondary one through the mech-

anism of being one of the causes of atherosclerosis. In 1906 F. P. Nunneley, of St. George's Hospital of London, published a book entitled *Aneurysms of the Abdominal Aorta* in which he limits the causes of aneurysm to atheroma, hypoplasia, congenital defects, trauma and hypertension. He lists the causes of atheroma as gout, syphilis and alcoholism. This book was based on autopsy examinations of 32 cadavers in which aneurysm was found. It is most interesting that the location of abdominal aortic aneurysm above the celiac axis was found in equal numbers to those located in the last three inches of the aorta. He noted that rupture was far more likely in an aneurysm located in the abdominal aorta than in the thoracic aorta.

In 1906 a fairly long list of contributors to the literature concerning treatment of aneurysm was available to Nunneley. Some of these were surgical some medical, most of them nonsense as we see them now. Valsalva had nothing more to recommend for patients with symptomatic aneurysms than the placing of the patient and his circulation in a state of almost deathlike rest with bloodletting, very restricted diet and total bed rest for long periods. His basic idea was logically expressed as being designed to produce a clot within the aneurysm, thereby inactivating it. In France, Lancereaux extended this aim in 1897 by the subcutaneous injection of gelatin with the idea that it would increase the blood's coagulability.

One of the hard-to-believe mechanical means of dealing with abdominal aneurysm was introduced by Murray of Newcastle in 1864. This consisted of the application of a tourniquet to the abdomen, tightening it until all pulsation ceased in the vessel. Two periods of compression were used in his first case, lasting two and five hours respectively. The first treatment had no effect but the second resulted in permanent cessation of the pulsation. It is almost impossible to credit the results claimed – that the patient lived for six years thereafter in good health and then died of rupture of a second aneurysm, the first said to have been resolved into a fibrous mass, as was found at autopsy. In his famous surgical textbook, Keane suggested that this compression for abdominal aneurysm should be done with a clamp applied directly to the aorta above the aneurysm after a preliminary laparotomy, the clamp being removed after a period of time, and the abdomen closed. There is no evidence that Keane himself ever did this and undoubtedly this is further evidence of his good surgical judgment.

Proximal ligation was applied to intra-abdominal aneurysms by Astley Cooper in 1828. The aneurysm was located entirely within the abdomen but was actually of the external iliac artery. Death occurred in this case 40 hours after the operation, due to tearing of the ligated vessel. In the interim before death, pulsation ceased, the mass decreased in size and there was not an inordinate deterioration of circulation in the limb. John Hunter had applied the same technique in 1785 in popliteal aneurysms. Part of Hunter's fame is based on this application of a concept, in spite of the fact that Anel had used proximal ligation for popliteal aneurysm in 1710. Actually, in addition to this priority in time, Anel's thinking was superior because he insisted that the tie be placed as close to the sac as possible to protect the function of the branches of the proximal artery. In 1906, Nunneley was able to accumulate a list of 14 instances in which various surgeons, including Cooper in 1828, and James Murray and Watson, had done proximal ligation for anuerysm of the abdominal aorta itself. The list is both impressive and convincing in that the mortality from the surgery was 100 percent. The longest survival among these was one reported by Keane in a case of ruptured aneurysm in which the patient survived for 48 days.

In 1864 a newer method of management was introduced by Moore. This consisted of threading a fine wire into the lumen of the aneurysm, and in his first case Moore passed 78 feet of spiraled wire into the sac of an aneurysm attached to the ascending aorta. In the next 10 years this technique was misapplied to nine

cases of abdominal aorta. In spite of the fact that these were not saccular aneurysms, cure was claimed in two patients, the others succumbing to the operative procedure or to cardiopulmonary complications following it. This technique was extended in 1879, on the suggestion of a surgeon named Corriadi who recommended that the clot in the meshes of the wire might be hastened by warming the wire with an electric current. The method was used by Finney twice in this country at the Johns Hopkins Hospital, each time with fatal results. Surgeons either quit using the method or quit reporting it until it was seemingly rediscovered in the early 1950's. I had the privilege at about this time of helping Lester Dragstedt do a percutaneous puncture of a large saccular thoracic aneursym. He introduced about 50 feet of tightly twisted insulated wire into the sac and then passed a current through it. I also was privileged to be in the patient's room in the afternoon several days later to witness the unforgettable event of the sac's rupturing to the outside, in the region of the needle puncture site, a spectacle equalled only by Old Faithful.

Matas was the most emphatic of those who realized that the only possible application of this means of producing intra-aneurysmal clotting was in saccular aneurysms. This of course was in keeping with Matas' track record in fathering the first truly reconstructive operation for peripheral arterial aneurysms, an outgrowth of his obliterative endo-aneurysmorrhaphy. Although he was undoubtedly quite right in not trying it in abdominal aneurysms, his pioneering in femoral, popliteal and brachial lesions with reconstruction was one of the remarkable contributions made by this man.

In 1952 all of the elements were available for someone to resect and replace with a graft an abdominal aortic aneurysm. Brach, in England, and Gross, in this country, had demonstrated by their work on coarctation that the aorta could readily be clamped temporarily without damage. Gross had used homologous aortic segments in reconstructing a number of anatomically difficult coarctations. After a long and difficult history, suture techniques and materials had been developed for blood vessels, and there was a good body of work available having to do with implantation of autogenous saphenous veins and homologous arteries in peripheral locations for the relief of arteriosclerotic obstructions.

Doctor Dye and I were by this time in the midst of a surprisingly successful series of femoral-femoral and femoral-popliteal bypasses using vein grafts. Together with John Olwin, who made significant contributions to this work, and Max Sadove, whose help was indispensable, we had put in some 30 vein bypasses and had presented the series at the American Surgical Association in 1952. At the time of this presentation John Olwin, in discussion, presented our first case of resection of the aortic bifurcation for Leriche syndrome with insertion of an homologous aortic bifurcation graft, which had been done in March of 1952. At that time we were unaware of the previous work of Oudot, who, beginning in November of 1950, produced normal flow into the lower extremities by an aortic homologous graft in three patients. He had reported this in 1951 in Europe.

Two things, therefore, had prepared us for resection and graft of an abdominal aneurysm. One of these was the several dissections which we had done in clinical cases about the aorta proximal to an abdominal aneurysm in order to wrap the aorta at this point with cellophane. This had been done in the hope that the scar tissue produced by the cellophane would gradually diminish the lumen, or even occlude it above the lesion; actually it taught us that a segment of virtually normal aorta was available, in many cases, between the renal arteries and the proximal end of the aneurysm. We were encouraged that such an aorta would hold sutures, by the previous work of Bahnson who had directly removed saccular aneurysms of the thoracic aorta by lateral aneurysmectomy. Resection of our first aneurysm in 1953 was pure labor. At that time and for some

years afterwards we thought it important to remove the damaged aorta in its entirety.

This lead us repeatedly to enter the vena cava and to spend long periods of time searching for and controlling all of the lumbar arteries communicating with the aneurysm from outside the lesion. Our first resection was preceded, by almost a year, by a similar resection of Dubost's in France.

Before long we had more aneurysm cases on hand than we had homologous grafts, and from time to time a small waiting list would develop; some of these cases were patients who aneurysms were symptomatic, and who were quite likely to know that their lives were threatened. One patient in particular appeared to be dissatisfied with this situation. He happened to be a police sergeant in Peoria where the police had learned to be quite tough because of their high concentration of breweries. At any rate, after waiting for a period of time because of the lack of graft, this man told Sam* and me that if we didn't provide him with his substitute artery pretty soon he would go out and shoot his own. He was, of course, moved higher on the list to prevent a hunting season, but many times thereafter we considered calling on him when we became desperate for a supply of vessels. We presented this case together with our statistics on aortic bifurcation grafts in Leriche syndrome, at the 1953 meeting of the American Surgical Association. During this presentation we made no reference to the work of Dubost because we had no knowledge of it, but in the published paper, proper credit is given to him. DeBakey was in the audience in 1953, and he immediately went home and began a series which, within the next year, grew to amazing proportions, later proving to be the largest, and beyond a doubt the most successful in terms of low mortality, that exists to date.

The first aneurysms in our series were operated upon at the Hines Hospital and at the University of Illinois hospital. It was about number five which was done at St. Luke's Hospital, and a high proportion of the earlier aneurysm resections were performed when we went as a visiting team to other hospitals, ranging as far away as Gary, Indiana. I have a favorite memory of one done at a very early date in Gary. Sam,* Max Sadove, and I drove out to Gary in the very early hours and started to work at eight in the morning. The resection and graft, characteristically for that time, took 11 hours, but in spite of considerable fatigue we drove home a happy group.

In the ensuing years I must admit that we were not sufficiently devoted to keeping an isolated full record of the abdominal aneurysm cases. Indeed, sometime in 1955 our current list was lost. Dealing as we were, with at least a portion of our patients in a transient population at the Illinois Research and Education Hospital and Hines Veterans' Hospital, it is quite likely that some of the early cases are not included in our present data. This cannot have produced a deficiency in our surgical mortality figures, because of the existence of autopsy records and separate lists of patients who died. However, with the assistance of a most skilled and diligent statistical secretary, we have in the past several years communicated with all known patients, and at this time I present to you the results obtained in 1007 abdominal aortic resections, absolutely consecutive in every sense, except probably for a few individuals, who have been excluded because, for one reason or another, every record of their having been operated upon no longer exists. The data includes almost 20 years of experience with this lesion. The operations themselves have been carried out by William S. Dye, Hushang Javid, James Hunter, Hassan Najafi, Marshall Goldin, and a long series of residents, as well as myself.

Throughout our development of this series, the indication for removal of an abdominal aneurysm has been simply its presence. This policy is strongly supported by reports during pre-resection days on

*William S. Dye

the longevity of individuals with untreated aneurysms. One series was reported in 1906 from three major London hospitals: Guy's, St. Bartholomew's and St. George's; 109 abdominal aneurysms were included. The longevity of these patients, all of whom were studied at autopsy, averaged 14 months from the date of detection. The range was 19 days to 9 years. Colt, in 1927, found the average duration of life to be one year after the appearance of symptoms. Campmyer, in 1936, studied 65 patients; 87 percent of these died in a period of less than one year after the development of symptoms, and death occurred within one month of hospitalization in 38 of the 65. Estes reported from the Mayo Clinic in 1950 that 33 percent of 102 patients were dead within one year of the discovery of an abdominal aortic aneurysm, whether it was symptomatic or not. A thoughtful rounding out of the statistics learned from these papers indicates that 60 percent of patients having abdominal aneurysm are dead within one year of the development of symptoms, 33 percent die within one year of the diagnosis having been made. In our series, diagnosis has been dependent upon physical examination, largely palpation. Plain x-rays of the abdomen may help because they show, in a very high percentage of cases, a line of calcification in the wall of the aneurysm. Aortography is of little use, because extremely few abdominal aortic aneurysms have within them a lumen much larger than that of a normal aorta due to the building up of mural clot. If we had done abdominal aortograms on every patient we would have avoided exploration for aneurysm in two patients whose abnormal physical findings were due to tortuosity, rather than dilatation of the aorta. Statistically, the errors in diagnosis had been inconsiderable. In two patients a disc or horseshoe kidney with an unusual amount of renal tissue in front of the aorta misled us into the diagnosis of aneurysm. But in a third patient with such a disc kidney there was also an aneurysm of significant size. One patient was operated upon for aneurysm who had a circumscribed mass of lymphatic metastases from a seminoma of the testicle, and another patient had a pancreatic tumor. A final patient, whom we will never forget, presented as an abdominal aortic aneurysm because of a rounded fibrous mass which was actually only omentum.

The technique of resection has changed during the development of the series in many ways. The principle of total resection of the aneurysm was abandoned in about 1962, when Hushang Javid very ingeniously simply opened and evacuated the aneurysm, removed all atheromatous material and, after suturing the graft into the opened defect, wrapped the remaining media and adventitia over the graft. This step forward saved many hours of surgical work thereafter. In the earliest graft implantation, an everting mattress suture was used in performing the proximal anastomosis between aorta and the homologous tissue then being used. In many instances a second layer of an over-and-over suture was placed in the everted edge. This technique was altered to a simple single layer of over-and-over suture even while we were still using homologous grafts, and, of course, only this kind of anastomosis can be made in the prosthetic materials now used.

The first prosthesis was homemade, on the sewing machine, from two layers of cloth taken from a tail of one of Sam's* best Dacron shirts. The greatest advance in prostheses occurred when bifurcated tubes of woven Dacron could be woven as such and then crimped to give them the much valued flexibility which facilitates implantation.

In summary, our material consists of 1007 cases (Table I) which can be divided into 844 in whom the operation was done electively and 163 in which it was done as an emergency for a ruptured lesion. Surgical deaths numbering 63 or 7.4 percent comprise those patients who died for any reason during the initial hospitalization or during a subsequent hospitalization due to a complication stem-

*William S. Dye

TABLE I

SUMMARY OF CASES

	Elective	Ruptured
Total operated	844	163
Surgical deaths	63 (17.4%)	66 (40.4%)
Died before 1971	286	37
Alive in 1971	411	51
Lost to study before 1971	84	9

ming directly from the resection. In the series of ruptured aneurysms, 66 of the 163 suffered a surgical death. This is 40.4 percent and compares very favorably with the slightly more than 50 percent mortality that existed some years ago at about midpoint in our series.

The prognosis after resection in a series of abdominal aortic aneurysms would be most accurately known if the study were made after all patients had finally died. Obviously, resection of an abdominal aortic aneurysm does not confer immortality on those who survive it. Indeed, in the age group in which we are working, it won't be long before the series I am now reporting could become such a perfect series. These data, however, were finalized some 18 months ago. At that time 286 elective patients and 37 in the ruptured group had already died. Still alive at sometime in 1971 were 411 elective and 51 ruptured patients. In 1971, a total of 93 patients could not be located. Quite a number of these, however, had been followed for long periods up to some date prior to 1971.

More succinctly, this table indicated that of the 1007 patients, 462 remained alive in 1971, 323 died on a known date before 1971, 129 died in the hospital, and 93 were lost to follow-up before 1971 (Table II).

The average longevity from the time of surgery to the date of death in 286 patients who have a complete follow-up is 46 months (Table III). Longevity, as far as it is known, of patients who were lost to follow-up before 1971 is presented in Table IV, including the ruptured and elective patients. The number in this group, as I said before, was 93, and by the calculations indicated here, the average survival known to us is 25.9 months. Lon-

TABLE II

ABDOMINAL AORTIC ANEURYSM CASES STUDIED

Surviving in 1971	462
Known date of death before 1971	323
Died in hospital	129
Lost to follow-up before 1971	93
Total	1,007

gevity to 1971 of patients known to be alive in 1971 is shown in Table V, with the elective and ruptured categories separated. Among the elective patients still alive, the average survival up until 1971 has been 52 months. Among the ruptured group it is very nearly the same, being 48 months. The ranges are also shown.

Some interesting differences exist in mortality and longevity when the patients are separated by sex. Table VI shows that 136 of our 1007 patients were female. There is a suggestion that the risk of aortic resection in females is greater than in males in the elective group. This difference, however, is not significant. There is,

TABLE III

LONGEVITY TO DATE OF DEATH IN 286 PATIENTS WITH "COMPLETE" FOLLOW-UP

Number of patients	286 Elective
Total months of survival	13,308
Average survival/patient	46 months

TABLE IV

KNOWN LONGEVITY OF PATIENTS LOST TO FOLLOW-UP BEFORE 1971

Ruptured and Elective Together	
Number in group	93
Total months of known life	2,408
Average/patient	25.9 mo.

TABLE V

LONGEVITY TO 1971 OF PATIENTS KNOWN TO BE ALIVE

	Elective	**Ruptured**
Total number of patients:	411	51
Total months of survival:	21,390	2,449
Average survival/patient:	52 mos.	48 mos.
Range in months:	6 to 204	60 to 120

TABLE VI

MORTALITY AND LONGEVITY BY SEX

	Female	Male
Number Elective	117	727
Number Ruptured	19	144
TOTAL	136	871
Surgical Deaths		
Elective	12 pts (10.2%)	51 (7.0%)
Ruptured	12 pts (63.1%)	54 (37.5%)
Survivors to 1971		
No. Survivors	58 pts	353 pts
Average Longevity	56.4 mos/pt	50.9 mos/pt
Average Longevity of patients dying before 1971 or lost to follow-up	54 pts 36.8 mos/pt	413 pts 42.2 mos/pt

on the other hand, a significant difference in the figures of 63.1 percent surgical deaths among females with ruptured aneurysms and 37.5 percent mortality among males in that category. The length of survival of patients not dying at the time of surgery is not significantly different on the basis of sex, either in the group of survivors to 1971 or in the group composed of both those who died before 1971 and those who were lost to follow-up.

The surgical mortality in the series has been related to age, expecting that the risk would be roughly proportional to age. Table VII, which contains few really significant entries, will serve a purpose, nonetheless. With groups composed by age at increments of five years from ages 40 to 85, the variation in mortality among elective cases is from 1.6 percent to 10.5 percent. The only statistically significant differences are two. The figure of 1.6 percent for the ages 51 to 55, compared to the mortality in every other group ranging from 6.0 percent to 10.5 percent, is significant. Otherwise the mortality among the groups of elective resections does not vary significantly. There is no apparent explanation for the low mortality in the 51-to-55 age group. The fact that patients from 75 to 85 years of age can be operated upon with the same risks as patients in any other group excepting the 51 to 55 is, I think, a testimonial for the quality of modern anesthesia and postoperative care.

The difference between the 16 percent mortality in the 56-to-60 group, and the 50 percent in the 81-to-85 group is insignificant because there are only four patients represented in the latter. The numbers in the 66-to-70 year age group were the same as in the group from 71 to 75: 35 patients. Hence, the calculated difference between 37.1 percent and 65.7 percent is significant. One cannot guess at the reason for such a difference. If a patient is to have an aneurysm undiscovered until the time it ruptures, he is far better off to be 56 to 60 years old than he is to be 71 to 75.

It is only because of some personal compulsiveness that we have tested the effect of the patient's age at the time of operation against his longevity if he survives the operation. Table VIII shows that when patients are grouped according to age at operation in five segments, each comprising an age spread of 10 years, there is an expected decay in long survivorship in those patients operated at more advanced ages. The satistical relationships among these figures is unknown, because every one would of necessity require comparison to some very compli-

TABLE VII

SURGICAL MORTALITY BY AGE

(844 Elective + 163 Ruptured = 1007 Total)

Age: Years	# Elective/Mortality		# Ruptured/Mortality	
Under 40	1	0	0	—
40-45	1	0	2	0
46-50	16	1 (6%)	5	2 (40%)
51-55	70	1 (1.6%)	12	4 (33.3%)
56-60	153	11 (7.2%)	25	4 (16%)
61-65	179	14 (11.7%)	28	9 (32.1%)
66-70	202	17 (8.9%)	35	13 (37.1%)
71-75	147	12 (8.2%)	35	23 (65.7%)
75-80	56	5 (8.9%)	16	9 (56.2%)
81-85	19	2 (10.5%)	4	2 (50%)
85 +	—		1	0

TABLE VIII

AGE AT OPERATION VERSUS LONGEVITY OF SURVIVORS

	50 or Less	51-60	61-70	71-80	81-90	TOTALS
Number operated:	23	260	444	254	24	1007
Surgical deaths:	3	20	53	49	4	129
Survived 6 mos. or less:	3	26	38	22	1	90
Survived ½ to 3 years:	10	86	161	101	10	368
Survived 3 to 5 years:	5	68	72	50	7	202
Survived 5 to 9 years:	2	49	73	22	2	148
Survived 9 to 12 years:	2	5	33	7	0	47
Survived 12 years +:	0	6	14	3	0	23

Includes Elective & Ruptured:
1) Alive 1971 = 462)
2) Died before 1971 = 323) 878 Survivors
3) Lost to follow-up = 93)

cated life-expectation tables. Emotionally, however, it is encouraging to note that among 254 patients operated upon between the ages of 71 to 80 after an original surgical mortality of 49 patients, three survived for periods ranging above 12 years. Various other superficial analyses of this table could be made. It is necessary to point out, however, that at this time one is unable really to gauge the effect on lifespan of a successful operation for an abdominal operation at any specific age.

The greatest possible emphasis however, should be placed on the general comparison of the outlook of patients with abdominal aortic aneurysms who are neglected after their lesion has been discovered and those who are subjected to an operation. Only sympathy is due to the patient who suffers a rupture of an aneurysm known to his doctor and, perhaps, to himself for months or years. Something, no doubt, is due such a patient who has been subjected to months or years of cliff-hanging before he is finally sent for surgical treatment of a known aneurysm. Only education of the medical population will reduce the risk attendant on procrastination after the diagnosis of abdominal aneurysm has been made.

HIRSUTISM: A DIAGNOSTIC CASE STUDY

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ABSTRACT. A 22-year-old, ammenorrheal, hirsute and virilized female whose urinary 17-ketosteroid levels and plasma androgen concentrations were consistently in the low normal range for females was intensively studied. Femoral vein catheterization with selective sampling of blood from the left adrenal and left ovarian veins permitted documentation and localization for the first time in this patient, of excessive testosterone concentration (1425 ngm percent) in the ovarian vein plasma. Wedge resection of both ovaries resulted in reduced levels of plasma androgens, restoration of regular menstrual cycles, and some decrease in hirsutism. It is stressed that early diagnosis and specific treatment with an aim at prevention of hair growth results in optimal clinical benefit.

INTRODUCTION

Hirsutism like an iceberg may be the only visible tip of widespread disease which is or will become manifest in female patients. Too frequently, however the hirsute patient is released from the physician's office with the comforting diagnosis of constitutional or idiopathic hirsutism, armed with the reassurance that nothing really serious is wrong. Even in this day when long hair is highly sought by both sexes, the female face and other regions of the body are considered inappropriate places for hair. To most women what more serious a problem could exist than profuse facial hair? The medically serious problems often associated with hirsutism such as obesity, amenorrhea, infertility, and even tumor may be considered minimal from her viewpoint.

The patient to be presented was studied several times at Cook County Hospital (CCH) as well as at Rush-Presbyterian-St. Luke's Medical Center (RPSLMC) before the source of her supply of androgens could be identified.

CASE HISTORY

S.R., a 22-year-old black female, whose gravidity and parity were zero, was admitted to Rush-Presbyterian-St. Luke's Medical Center (RPSLMC) on February 27, 1971, for evaluation of a three and five year history of amenorrhea and hirsutism respectively. Menarche began at age 17, in 1966, with periods occurring irregularly every three to four months. Menstrual flow was prolonged, 14 to 21 days, and

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often excessive, 12 pads per day. She had a dilatation and curettage in September 1968 for menometrorrhagia followed by a single normal period in October 1968. Efforts to cycle her with birth control pills and progesterone during the latter part of 1970 were unsuccessful. Pelvic examination as reported in her chart at Cook County Hospital (CCH) was as follows: (1) clitoris was enlarged, (2) right ovary was not palpable, and (3) left ovary 3 x 2 x 1 cm. She was also reported to have galactorrhea and extensive hirsutism. Available laboratory data from the May 1970 CCH admission are summarized in Table 1.

The patient was next seen at RPSLMC in May 1971, where again her pertinent physical findings were a possibly enlarged left ovary, an enlarged clitoris, and extensive hirsutism involving her abdomen, chest, entire facial and sacral areas. The galactorrhea spontaneously subsided when previously prescribed chlorpromazine was withdrawn. The laboratory data obtained during this admission are also summarized in Table 1. Roentgenograms taken of the patient's chest and skull were read as normal. In spite of enlarged ovaries as revealed by pneumogynecography (Fig. 1), ovarian biopsy under laparoscopic control did not support a diagnosis of Stein-Leventhal syndrome. The patient was placed on prednisone 5 mg twice daily; however, she returned only once for follow-up.

Because of menometrorrhagia and lower abdominal pain she returned to the RPSLMC emergency room in May 1972, at which time another dilatation and curettage was performed. Subsequent laboratory tests, obtained during her third admission in August 1972 are summarized in Table 1. Because her 17-ketosteroid and plasma androgen levels remained in the low normal range on all occasions when tested, it was decided to try to define the source of her androgens by employing more elaborate studies. Percutaneous femoral vein catheterization was performed and plasma samples from the inferior vena cava, left ovarian and left adrenal veins were obtained. Testosterone concentrations in these three efferents were determined (Table II). While awaiting the results from the first femoral vein cathterization study, the patient was placed on dexamethasone 1.5 mg at bedtime and 0.5 mg on awakening each day (a total of 2 mg/day). In November 1972, a second catheterization study was performed while the patient remained on dexamethasone suppression. These results are also summarized in Table II. Because of increasing abdominal pain and inadequate response to steroid suppression, wedge resection of both ovaries was performed. Four grams of tissue were removed from the right and two from the left ovary. Testosterone concentration determined on a sample of blood obtained from the left ovarian vein at surgery was 1425 ngm

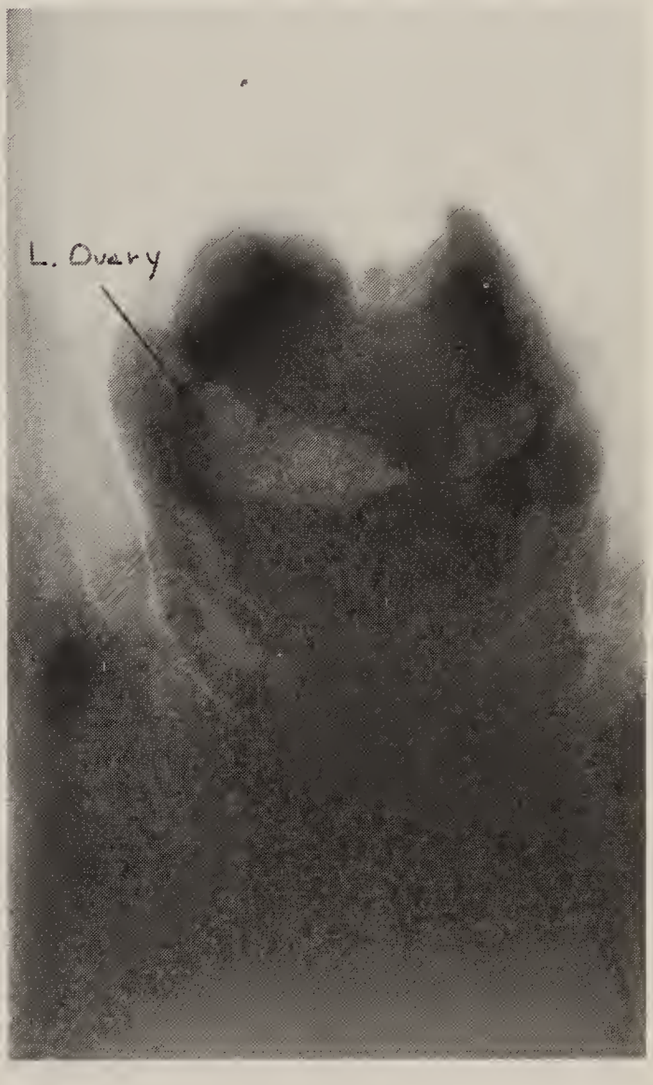

Fig. 1—Pneumogynecography of the patient. The enlarged left ovary appears larger than the uterus (center). The right ovary is difficult to evaluate because of the more polar projection.

TABLE I

A Summary of Steroid and Gonadotropin Results From All Hospital Admissions

DATE	REMARKS	← urine → 17-OH	17-KS	← plasma → Cortisol	T*	A*	E_1*	E_2*	FSH*	LH*
		Normal Values								
		mg/24 hrs		µg%	ng%	ng%	ng%	ng%	mIU/ml	mIU/ml
		3-12	6-13	6-27	>100	90-280	3-16	3-30	2-50	5-100
3/5/70	Baseline	4.9	5.1	13.0 am						
3/6/70	Baseline	4.1	9.2	19.0 pm						
3/1/71	Baseline	5.9	6.8	29.2 am	51					
3/5/71	Baseline	7.5	3.2	13.2 pm						
8/3/72	Baseline		6.8	11.8 am	58	160	23.5	24.4	6	31
8/4/72	Baseline		11.8	6.2 pm	29		11.9	21.2	4	17
8/6/72	Dexamethasone 2 mg		6.6		13	196				
8/8/72	Dexamethasone 8 mg		6.7	2.5 am		184	16.7	21.0	9	14
8/11/72	Dexamethasone 8 mg HCG* 5,000 u		5.9	6.9 am	53	160	16.9	41.7		
11/13/72	Dexamethasone 2 mg			<1.0 am						
11/16/72	Dexamethasone 2 mg		5.6	<1.6 pm						
11/17/72	Dexamethasone 2 mg		6.0		174					
11/28/72	Wedge Resection of Right & Left Ovary				1,425					
12/4/72					26					
12/5/72		5.9	4.3		16	140				
12/6/72		10.7	4.7		14	156				

* T = Testosterone; A = Androstenedione; E_1 = Estrone; E_2 = Estradiol;
FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone;
HCG = Human Chorionic Gonadotropin.

TABLE II

COMPARISON OF PLASMA TESTOSTERONE CONCENTRATIONS
IN PERIPHERAL VEINS WITH THAT IN ADRENAL AND OVARIAN VEINS

Date	Remarks	Peripheral Vein	Left Adrenal Vein	Left Ovarian Vein
7/13/72	*Normal Female	<100 Ng%		
	Baseline	58 Ng%	217 Ng%	>953 Ng%
11/29/72	**Dexamethasone 2 mg	79	115	7,398

*Similar catheterization studies and testosterone assays performed on three non-hirsute women revealed peripheral ovarian and adrenal vein testosterone concentrations all to be less than 42 Ng%.[1]

**Oral dexamethasone was administered for three months prior to this catheterization, 1.5 mg at bedtime and 0.5 mg in the morning.

percent. Post-operatively, peripheral plasma levels of testosterone decreased to low normal on three occasions when this steroid was evaluated.

Approximately four weeks following surgery, the patient's menstrual periods returned. These have occurred regularly during the ensuing six months and her abdominal pain has subsided. The rate of hair growth remains difficult to evaluate although the patient claims this has markedly decreased.

DISCUSSION

Evaluation of the patient with hirsutism should always begin with a carefully taken history. Age at menarche, information about menstrual periods, age at onset of hirsutism, prevalence of hirsutism in the family, and medications used by the patient may reveal important diagnostic information. A complete physical examination may suggest additional endocrinologic problems such as adrenal, pituitary, or thyroid disease in addition to gynecological abnormalities. A normal pelvic examination should not dissuade the physician from subsequent biochemical and histological studies as many patients with elevated androgen levels do not have enlarged ovaries when evaluated by laparoscopy.[2] In addition, enlarged ovaries very frequently remain undetected, even in non-obese women, even when pelvic examination is performed by experienced gynecologists. This may be due to the fact that very large ovaries may move out of the pelvis and thus out of reach on bimanual examination.

Laparoscopy remains an important part of the investigation of these patients because ovarian biopsy as well as a gross description of the ovary can be obtained. Characteristics of the capsule, size of the ovary, presence or absence of cysts and sites of ovulation are but a few of the interesting facts obtainable at laparoscopy.

Laboratory studies are an indispensable part of the diagnostic workup of these patients. The time-honored urinary 17-ketosteroid evaluation has mainly time and honor as its virtue and minimal diagnostic importance because frequently the values may be normal or even low normal, as seen in this patient. Peripheral levels of plasma testosterone and androstenedione are good indicators, if elevated, that excessive androgen is being secreted. However the localization of synthesis of these steroids should be determined by sampling efferent vessels of the ovary and adrenal via percutaneous femoral vein catheterization. This procedure may identify the source of androgen when peripheral levels are low. The procedure carries minimal morbidity and confirmed and localized for the first time in this patient the secretion of the androgens whose presence were clinically evident. Fractionation of urinary steroid metabolites has not been as helpful clinically as reports have suggested because normal concentrations of 11-hydroxylated steroid metabolites do not always rule out excessive adrenal production.

The clinical value of acute suppression and stimulation in these patients remains difficult to assess. Certainly lowering of 17-ketosteroids and plasma androgen by dexamethasone treatment and elevation of the same following gonadotrophin injections suggest that feedback systems are intact. But which organ is responding primarily to these drugs is impossible to determine by sampling only peripheral blood and urine. Data obtained during recent catheterization studies in this hospital suggest that ovarian tissue on occasion may be responsive to adrenocorticotropin (ACTH) as well as adrenal cortical tissue. If further studies support these early findings the morning ACTH surge or other stress situations may, in patients with excessive androgen production by the adrenal or ovary, result in periodic elevation of androgen production. In addition, the relative security of the hospital setting to the hirsute woman may result in less ACTH release and therefore may suggest that adequate suppression by steroid therapy can be obtained when in fact after she is returned to her usual environment it has not been obtained. Thus more time

will be required to evaluate the acute suppression tests.

The estrogen levels should be assessed in these patients because free plasma androgens (the active form of the steroid, as contrasted to total plasma androgens) are increased when estrogen levels are low. Thus borderline high levels of total androgen have more biological significance when accompanied by low plasma estrogen concentrations. Gonadotrophin assays have not been helpful in diagnosis or management of these patients thus far. Most patients do not have sustained elevated levels as reported to occur in patients with polycystic ovaries.[3] This may be in part because hirsutism and amenorrhea are associated with polycystic ovaries only one-half of the time. Certainly adequate levels of gonadotrophins are reassuring that hypopituitarism is not the cause of the amenorrhea but low levels do not necessarily reflect deficiency.

CONCLUSION

Women with hirsutism of recent onset deserve careful consideration of their problems, as prevention is the only adequate assistance that can be offered. Once terminal hair growth is established the main avenue of help for these women can only focus on preventing additional involvement of old areas as well as the initiation of new areas. The management of hirsutism like many other medical problems demands prompt investigation and appropriate treatment with an aim at early prevention. Once the source of androgen production is discovered and arrested, some regression of hair growth may be expected. However, mechanical methods of removal such as electrolysis may still be required in advanced cases.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Marc Pomerantz for his assistance with this patient's case.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Cardiology

Hauser RG, Carleton RA: The failing myocardium. II. Assisted circulation. *Med Clin N Amer 57:187, 1973*

Mechanical circulatory assistance has been the object of intensive laboratory and clinical investigation during the past 15 years. Various devices based on four fundamental methods to augment cardiac function and improve peripheral organ perfusion have been described. The benefits of mechanical assistance in the management of low cardiac output states during the perioperative period of open-heart surgery or cardiac arrest have not been proved. Of those methods available for temporary circulatory assistance for shock following acute myocardial infarction, only intra-aortic balloon pumping is physiologically sound, relatively safe and atraumatic, and adaptable for rapid employment in the coronary care unit. However, skilled personnel are required. Although intra-aortic balloon pumping appears to provide real circulatory assistance, it has not clearly modified the survival rate of patients with cardiogenic shock. Therefore, this technique, though available commercially, remains experimental. At the present time no circulatory assist device can be recommended for severe myocardial failure and shock except in the setting of careful investigative trials.

Hauser RG, Nelson RM, Javid H, Blatt SJ, Toronto AF, Frank G, Long ML, Peacock HC: Clinical evaluation of the Dow hollow fiber membrane oxygenator. *Circulation, Suppl II, Vol. 45 and 46:II-3, 1972*

This membrane oxygenator (MO) was used in 20 patients (Pts) for total bypass (TBP) in an initial comparative trial with six Pts supported by disc (DO) and seven Pts supported by Bentley (BO) oxygenators. The MO circuit employed venous and artificial filters. Gas exchange, blood cell trauma, coagulation effects, proteins (SP), electrolytes (SE), enzymes (SZ) and renal function (RF) were evaluated before, during and after TBP through day ten. Means for arterial pO_2/pCO_2 during the total bypass were 374/35 MO, 132/21 DO, and 146/25 mm Hg BO.

Plasma hemoglobin levels (after mean TBP times for MO, DO, BO, of 92, 90 and 97 minutes) reached 31.6 MO, 59.0 DO and 15.4 mg percent BO.

Platelet counts always fell during TBP; mean values ($\times 10^3$) before and during TBP were 259→76 MO, 186→117 DO, and 251→114/mm^3 BO. The lower MO values are significantly different. Minimal inlet thrombosis was detected in the MO clotting times, factor II, V, VII and X measurements, euglobulin lysis, SP, SE, RF, SZ and bilirubin were not different. Oxygenator prime cultures were sterile.

The MO employed in this study provides excellent gas exchange, is suitable for human TBP, and warrants further study.

Long ML, Javid L, Hauser RG: Complication of central venous pressure monitoring: Cardiac arrhythmias and conduction disturbances. *Heart & Lung 2:416, 1973*

Central venous catheters are commonly used for clinical purposes, including pressure

monitoring. The hazards of central venous catheterization have been reported previously. However, this communication demonstrates a life-threatening disturbance of cardiac rhythm and intraventricular conduction associated with improper central venous catheter insertion. Correct placement may be performed safely provided catheter insertion is performed with continuous ECG monitoring and location confirmed by chest x-ray.

Susmano A, Carleton RA: Effect of antihistaminic drugs on hypoxic pulmonary hypertension. *Amer J Cardiol 31:718, 1973*

During exposure to 8 percent oxygen inhalation, 18 dogs experienced an average increase of 5.4 mm Hg in mean pulmonary arterial pressure. The administration of promethazine and chlorpheniramine during an initial exposure to hypoxia significantly decreased the pulmonary hypoxic pressor response; the administration of diphenhydramine did not. However, these three antihistaminic agents prevented the development of pulmonary hypertension during a second exposure to hypoxia ($P = 0.3 \times 10^{-6}$). Five dogs received progressive doses of chlorpheniramine, thus showing that the effectiveness of this drug can be demonstrated at a dose of less than 0.3 mg/kg body weight. The amounts of diphenhydramine and promethazine needed to achieve effectiveness equivalent to that of chlorpheniramine are sufficiently great as to restrict their applicability to man in acceptable doses. This study lends further support to the hypothesis that histamine mediates hypoxic pulmonary hypertension.

Susmano A, Passovoy M, Carleton RA: Comparison of the effects of two anesthetic agents on the production of hypoxic pulmonary hypertension in dogs. *Amer Heart J 84:203, 1972*

Inhalation of 8 percent oxygen produced pulmonary hypertension in only 13 of 22 dogs anesthesized with pentobarbital. Conversely, each of the dogs anesthesized with a mixture of droperidol and fentanyl developed hypoxic pulmonary hypertension ($p = 0.0055$), with an increase in the average mean pulmonary artery pressure from 9.7 ± 0.55 (S.E.) to 13.2 ± 0.77 mm Hg. The average calculated pulmonary arteriolar resistance increased from 280 to 353 dynes-sec-cm^{-5} without significant change in the pulmonary arterial wedge pressure. This analgesic-neuropleptic combination provides satisfactory anesthesia for studies of hypoxic pulmonary hypertension in dogs.

Susmano A, Passovoy M, Carleton RA: Role of hypercapnia in pulmonary hypertension. *Clin Res 21:673, 1973*

Increased pulmonary hypertension (PH) occurs in patients with chronic obstructive lung disease (COLD) during hypoxemia and hypercapnia. We previously showed that antihistamines block hypoxic PH. This study was done to clarify the roles of histamine, serotonin, and acidemia in PH induced by hypercapnia. Eighteen anesthetized (droperidol-fentanyl) intubated dogs (14 to 23 kg) spontaneously breathed room air and then a mixture of 10 percent CO_2, 20 percent O_2 and 70 percent N_2 (CO_2). After stabilization during hypercapnia, three groups of six dogs received respectively 20 mg of chlorpheniramine (CP), 5 μg/kg of methysergide (M), or sodium bicarbonate (HCO_3) into the pulmonary artery (PA) to correct the base deficit. CO_2 breathing significantly increased arterial pO_2 by 41 mm Hg, pCO_2 by 28 mm Hg, cardiac output (CO) by 0.7 L/min and mean PA pressure by 2.5 mm Hg. Arterial pH fell 0.2 ($p = .2 \times 10^{-8}$). Heart rate, PA wedge (W) pressure and pulmonary vascular resistance (PVR) did not change. No changes occurred with M. CP reduced W by 0.5 mm

Hg ($p = 0.4$), PA by 1.5 mm Hg ($p = .08$) and CO by .73 L/min ($p = .09$), without PVR change. HCO_3 (50 to 75 mEq) increased pH by 0.115 ($p = .00009$), CO by 1.3 L/min ($p = .007$) and PA by 1.2 mm Hg ($p = .01$), without W change; PVR fell ($p = .005$). Hypercapnia and acidemia did not increase PVR; PH reflected increased CO. Correction of pH with HCO_3 decreased PVR, suggesting that the increased CO masked a slight effect of pH on PVR. Serotonin or histamine blockade did not affect hyerpcapneic PH. The PH of defective ventilation in COLD reflects alveolar and arterial hypoxia with little contribution from hypercapnia or acidemia.

Metabolism

Becker FO, Eisenstein R, Schwartz TB, Economou SG: Needle bone biopsy in primary hyperparathyroidism. *Arch Intern Med 131:650, 1973*

Results of diagnostic needle bone biopsies in 25 patients subsequently undergoing neck exploration for parathyroid disease are reported. Histologic changes believed to represent hyperparathyroidism in bone biopsy specimens included evidence of (1) increased osteoblastic activity; (2) increased osteoid formation; and (3) excessive osteoclastic activity. Such changes were seen in 23 of 25 biopsies. The results of two biopsies were negative.

A positive correlation between pathologic findings in bone and surgically proven primary hyperparathyroidism was noted in 20 of 25 patients. Nine of the patients with abnormal biopsies had hyperparathyroidism, despite normal roentgenograms and alkaline phosphatase levels. Explanations accounting for abnormal biopsies in three patients with negative results for neck exploration were available. Two patients with proven parathyroid adenoma had negative results for bone biopsies. With proper interpretation, needle bone biopsy is a useful tool for evaluation of primary hyperparathyroidism.

Becker FO, Schwartz TB: Normal fluoride 18 bone scans in metastatic bone disease. *JAMA 225:628, 1973*

The occurrence of metastatic bone disease is proved by needle bone biopsy in two patients with negative fluoride 18 bone scans and bone roentgenograms. Hypercalcemia suggested the possibility of metastatic disease.

Nephrology

Couser WG, Stilmant M, Lewis EJ: Experimental glomerulonephritis in the guinea pig. I. Glomerular lesions associated with antiglomerular basement membrane antibody deposits. *Lab Invest 29:236, 1973*

Studies of nephrotoxic nephritis have demonstrated that antibody to glomerular basement membrane (GBM) induces experimental glomerulonephritis through complement- and polymorphonuclear leukocyte-mediated mechanisms. Recent observations suggest that glomerular damage induced by anti-GBM antibody may also be mediated through other mechanisms. The immunopathogenesis of anti-GBM nephritis was studied in guinea pigs actively immunized with human GBM in complete Freund's adjuvant.

Renal tissue, serum samples, and eluates were studied by routine histologic and immunofluorescent techniques. Animals injected with complete Freund's adjuvant alone served as controls.

Thirty percent (25/85) of immunized animals developed heavy proteinuria, but all animals studied (17 proteinuric and 33 nonproteinuric) had intense linear deposits of IgG anti-GBM antibody documented by elution studies. Some animals in each group also had circulating anti-GBM antibodies. The antibody deposits were composed largely of $\gamma 2$ with variable amounts of $\gamma 1$ and IgM. Small amounts of complement were deposited in two-thirds of the animals studied and did not correlate with the presence of proteinuria. Five animals had heavy proteinuria without detectable $\beta 1$C-globulin deposition. Furthermore, deposited, circulating, and eluted anti-GBM antibody from both proteinuric and nonproteinuric animals did not fix complement *in vitro*. Histologically, proteinuric animals had mild, focal glomerular changes without an inflammatory exudate and a marked decrease in glomerular Alcian Blue staining compared to nonproteinuric and control animals.

The absence of complement deposits in some proteinuric animals, lack of correlation between complement deposits and proteinuria, failure of antiGBM antibody to fix complement *in vitro,* and the bland nature of the glomerular lesion suggest that anti-GBM antibodies mediate glomerular damage in this model through complement-independent mechanisms. The histochemical data suggest that these mechanisms may involve alterations in glomerular sialoprotein.

Gray GW, Rennie IDB, Houston CS, Bryan AC: Phase IV volume of the single-breath nitrogen washout curve on exposure to altitude. *J Appl Physiol 35:227, 1973*

Phase IV volumes of the single-breath nitrogen washout curve were measured as an index of pulmonary interstitial fluid volume at ground level and after exposure to altitude. In a four-hour exposure to 16,000 feet in a decompression chamber, no significant change was found in the phase IV volume or the phase IV/vital capacity ratio, in five subjects. In 12 subjects exposed to 17,500 feet on Mount Logan, no significant change was seen in phase IV volumes after one week. It is concluded that no measurable increase in the pulmonary interstitial fluid volume, as detected by this technique, occurred with altitude exposure at the time intervals in which it was measured.

Kovithavongs T, Becker FO, Ing TS: Parathyroid hyperfunction in acute renal failure: Serial studies in man. *Nephron 9:349, 1972*

Serial serum parathyroid hormone values were determined in four patients with acute renal failure. They were found to be moderately elevated and in general correlated with hypocalcemia.

Nuclear Medicine

Shirazi PH, Stern AJ, Sidell MS, Rayudu GVS, Fordham EW: Bone scanning in the staging and management of bronchogenic carcinoma: Review of 206 cases. *J Nucl Med 14:451, 1973*

Total-body skeletal scanning with ^{18}F is an extremely sensitive indicator of metastatic bone disease. The purpose of this study is to evaluate the incidence of skeletal metastases in both untreated and treated bronchogenic carcinoma and to emphasize the need for

bone scanning to augment the initial clinical staging and subsequent management of this disease. Two hundred, forty-six scans were performed on 206 patients with bronchogenic carcinoma. Scans were interpreted by several observers and were classified as (A) absolutely positive for metastatic disease, (B) equivocal, and (C) definitely negative. Scan interpretations of preoperative patients were then compared with the clinical staging derived before scanning from roentgenograms, bronchoscopy/mediastenoscopy, and clinical findings. Patients who had already been previously treated by surgery, radiation therapy, chemotherapy, or a combination thereof were scanned to assess presence or progression of metastatic disease and response to therapy.

Of 114 preoperative or initial workup scans, 52 (46 percent) were positive and 9 (8 percent) were equivocal. When compared to the clinical staging (determined before bone scan), a high percentage of positive scans was found. Staging according to Clifton revealed the following percentages of positive scans: Stage I, 32 percent (12/37); Stage II, 50 percent (13/26); Stage III, 64 percent (11/17), and Stage IV, 49 percent (16/34). Using the classification system of the California tumor registry, positive scans were found as follows: localized disease, 37 percent (14/38); regional disease, 51 percent (18/35); and remote disease, 49 percent (20/41). The particularly high incidence of positive scans in the categories of Stage III and regional disease may reflect the inclusion of oat cell carcinoma within these categories.

Ninety-two patients who had already been treated with either surgery, radiation therapy, chemotherapy, or a combination thereof were scanned at varying intervals following therapy. Approximately 60 percent (55/92) of these scans were abnormal and 9 percent (8/92) were equivocal. Of 40 repeat scans, a high percentage (75 percent) showed either the appearance of new lesions or the progression of previously noted lesions.

It is apparent that the bone scan is an imperative requirement for accurate preoperative staging and treatment of bronchogenic carcinoma. In patients who are either postsurgical or who have had radiation and chemotherapy, the bone scan represents a sensitive means of assessing response to therapy and progression of metastatic bone disease.

Neuropsychiatry

Peters J: A synthetic perspective in neuropsychiatry. *World J Psychosyn 5:33, 1973*

A synthetic perspective in neuropsychiatry deals with the mind-body problem as one on which the medical specialist in neurology and psychiatry orientates his clinical approach. The paper develops its eclectic perspective on the mind-body problem by incorporating views of Thomas Hobbes, Sigmund Freud, and the phenomenologists. One of the major conclusions of the paper is to advocate the approach of Carl Rogers as a critical method in practicing organo-dynamic neuropsychiatry.

Orthopedics

DeWald, RL: Scoliosis. From *Practice of Surgery, Orthopedics 1, Hagerstown, Harper & Row, Publishers, Inc., 1972, Chap. 7N, pp. 1-39*

Scoliosis, a lateral curvature of the spine with vertebral body rotation, is a serious orthopedic affliction. The most common type affects adolescent girls who are otherwise fit and healthy. Early diagnosis and prompt treatment make it possible for most children with scoliosis to have a fairly normal-appearing posture and avoid catastrophic deformities.

The incidence of scoliosis has been studied by several investigators. Shands and Eisberg concluded from their analysis of 50,000 minifilms taken in a survey of chest diseases that 1.9 percent of the population over 14 years of age had a scoliosis of at least 10° and that 0.5 percent had a scoliosis of 20° or more. Wynne-Davies surveyed the family incidence of scoliosis among pupils in Edinburgh schools and nursery schools and in patients seen in infant clinics. In her classification of late-onset curvature in children eight years of age or older, she found an incidence of 1.8 per 1,000. Interestingly, the incidence of scoliosis among relatives of the index patients ranged from 26 to 4 times as high as in the corresponding general population, depending on closeness of relationship. Kane and Moe found a prevalence rate of scoliosis of at least 0.133 percent in Minnesota. All investigators found a higher incidence in females than in males in a ratio of 5:1.

There are two types of scoliosis: functional and structural. Structural scoliosis is any curvature of the spine with asymmetric side bending and fixed rotation. Functional scoliosis is any curvature of the spine without structural changes, e.g., scoliosis associated with a short leg.

Galante JO: The arthritic hip. *Int Surg 58:1 (Editorial), 1973*

The use of total hip prostheses has opened an entirely new approach to the field of hip joint reconstruction. Removal of the joint surfaces and replacement by artificial components brings about complete relief of arthritic pain. Firm fixation of the prosthetic device to bone by the use of methylmethacrylate is the one single feature that has made the procedure so successful. The results of this type of surgery are unparalleled by any other forms of hip reconstruction. Consistently successful results on over 90 percent of operated patients have been reported.

There are, however, potential problems that limit the scope and the indications for the procedure. These relate primarily to the long-term performance of the prosthetic devices. The issue of the effects of long-term implantation of plastics in the human body, the mechanical failure of prosthetic components after many years of active use, and the reaction of tissues to the products of wear (particles) are some of the sources of concern. For that reason total hip prostheses are usually not performed in young active individuals with normal life expectancy. The next few years will witness many improvements in prosthetic design, but particularly in the development and application of biomaterials with superior characteristics.

Kuettner KE, Wezeman FH, Simmons DJ, Lisk PY, Croxen RL, Soble LW, Eisenstein R: Lysozyme in preosseous cartilage. V. The response of embryonic chick cartilage to antilysozyme antibodies in organ culture. *Lab Invest 27:324, 1972*

Specific antilysozyme antibody was added to cultures of chick embryo femora in order to demonstrate the effects of such antibodies on the explants. No cytophathic effect was observed. If ^{14}C-lysine was added and quantitative autoradiography, analysis of immunoprecipitin lines in a living radial immunodiffusion preparation, and electrophoresis with autoradiography after elution from histologic sections were done, it was clearly demonstrated that the explants synthesized significant amounts of lysozyme. Quantitative autoradiography shows that addition of sufficient antilysozyme antibody to the cultures to completely complex all of the diffusable lysizyme in the tissue results in increased amounts of label in the tissue as compared with explants exposed to a control antibody. The label is particularly concentrated in the chondrocyte lacuna, the site where lysozyme is normally present in this tissue in highest concentration. Most likely, this increased radioactivity accummulates because of a barrier to diffusion formed by precipitin lines in the medium and fixation of antigen in the tissue by specific antibody. The data do not exclude the possibility that the addition of antilysozyme γ-globulin to the culture system results in enhanced synthesis of lysozyme by the tissue. If so, this suggests that there is a

feedback mechanism between chordrocytes and their surrounding matrix which influences the rate of synthesis of this cationic protein, which is at least partly regulated by the concentration of lysozyme in the matrix.

Lembert E, Galante J, Rostoker W: Fixation of skeletal replacement by fiber metal composites. *Clin Orthop 87:303, 1972*

Implantation of an open pore aggregate of sintered titanium fibers resulted in deep ingrowth of bone. Pore size variations of 190 μ to 390 μ did not affect the strength of fixation or the amount of bone penetration. The strength of fixation of sintered fiber metal implants after six weeks was found to be in the same range as that obtained using self-curing acrylic. The effect of weightbearing was studied in femoral head prostheses implanted in eight dogs. Fixation to the femur and bone ingrowth into the fiber metal composite were successfully maintained up to one year following implantation.

Mulcahy T, Galente J, deWald R, Schultz A, Hunter JC: A followup study of forces acting on the Milwaukee brace on patients undergoing treatment for idiopathic scoliosis. *Clin Orthop 93:53, 1973*

Forces acting on the mandibular, occipital, and thoracic pads were measured in patients in the Milwaukee brace. Measurements made for a group of seven patients wearing the newer throat mold design brace demonstrate factors important for patient selection as well as brace fitting and designs. In all activities, average longitudinal tractive forces were found to be less than those in previous studies of the conventional brace, (*e.g.*, 9.94 vs 1.13 kg in the standing position). The average tractive forces for the throat mold design brace were substantially lower (*e.g.*, 0.39 kg in the standing position). However, the relative change in the longitudinal tractive force magnitudes, during various activities were the same for all patient groups. Even though the tractive forces were different, the average forces acting on the thoracic pad were nearly the same in the conventional and the throat mold design brace. Among the groups of 30 conventional brace patients, larger tractive forces usually were present in patients with initially large curves.

Ray RD: Vascularization of bone grafts and implants. *Clin Orthop 87:43, 1972*

Vascularization of a devitalized implant, whether autologous or homogeneous, is delayed compared to vascularization of a living graft. Early vascularization is dependent not only on the viability of the graft, but also on its physical characteristics: cancellous bone grafts are vascularized sooner than cortical bone grafts. It would appear that active participation of the graft during the process of vascularization, either by attracting vessels or by direct anastomosis between the vascular channels of the graft and the host, is essential. When the graft cells are genetically related to the host, the host connective tissue cells participate in the subsequnt bone formation, apparently by induction, a type of induction that can be demonstrated within 10 days following transplantation. When the donor is not closely related genetically, a viable bone allograft is initially vascularized and then rejected. In the process of rejection the blood supply is lost and there is a cellular response on the part of the host. There are still many unanswered questions for further research on the process of vascularization of bone transplants.

Schultz AB, Larocca H, Galante JO, Andriacchi TP: A study of geometrical relationships in scoliotic spines. *J Biomech 5:409, 1972*

By the construction and manipulation of a mathematical analog of the human vertebral column, the changes necessary to bring a normal column into the geometrical configuration of idiopathic scoliosis were investigated. The following conclusions were drawn from the results:

(a) Asymmetry of the vertebrae was not required to reproduce the configuration of an early scoliotic curve.
(b) Mild scoliotic configurations appear achievable within the motion capabilities of the normal spine, without any alterations of the vertebrae themselves.
(c) Changes in the lengths of the anterior soft tissues did not play a role in the simulation of idiopathic scoliosis.
(d) Changes in the lengths of the anatomic structures running along the transverse processes and those in the region of the back muscles were necessary to reproduce the geometrical configuration of scoliotic spines.
(e) The frontal and horizontal plane rotations that occur in scoliosis combine in such a way as to tend to bring the tips of the spinous processes into a straight line in an AP view of the column.
(f) Regardless of the etiology a tethering tendency of the extreme posterior anatomic structures may be important in determining the complex configuration of a scoliotic curve.

Shimomura Y, Wezeman FH, Ray RD: The growth cartilage plate of the rat rib: cellular differentiation. *Clin Orthop 90:246, 1973*

Growth and cellular differentiation of the costochondral junction of the rat rib were studied using H^3-thymidine. Histologically, the cells of Ranvier's groove along with those of the germinative zone could be considered as being the source of cells for the other zones. The daughter cells of these two regions and not those of the *resting zone* contribute to the growth of the epiphyseal plate. Using H^3-thymidine, these observations were confirmed. Many of the cells, both of Ranier's groove and the germinative zone were heavily labeled within two hours after injection, whereas the cells of the *resting zone* showed only occasional labeling. Labeled hypertrophic chondrocytes were not observed until two days after injection and the label then persisted in this region for approximately 12 days. The preosteoblasts of the zone of erosion would appear to be derived from local connective tissues (labeled early following injection), by proliferation and modulation from the cells of Ranvier's groove, and also from the zone of hypertrophic cartilage.

Sorgente N, Hascall VC, Kuettner KE: Extractability of lysozyme from bovine nasal cartilage. *Biochem Biophys Acta 284:441, 1972*

Lysozyme (mucopeptide N-acetylmuramylhydrolase, EC 3.2.1.17) is present in the extracellular matrix of bovine nasal cartilage at a concentration of about 0.03 to 0.08 mg per g wet tissue (3 to 8 mg/100 ml per g). It is extracted from the tissue in guanidinium chloride solutions between 0.3 and 0.8 M. These concentrations are much lower than those which effectively extract most of the proteoglycans from the tissue, 2.5 to 3.0 M. Lysozyme migrates to the top of CsCl density gradients which are used to purify aggregated or monomer proteoglycan preparations; this suggests that lysozyme is not involved in the aggregation of proteoglycans *in vitro*. Chondroitinase from *Proteus vulgaris* effectively removes chondroitin sulfate from cartilage slices without solubilizing lysozyme which indicates that this highly anionic polysaccharide does not immobilize lysozyme in the matrix. Trypsin (EC 3.4.4.4) releases most of the chondroitin sulfate as well as 75 percent of the lysozyme from the matrix.

Otolaryngology and Bronchoesophagology

Azem K, Caldarelli DD: Sudden conductive hearing loss following sneezing. *Arch Otolaryngol 97:413, 1973*

This is a case report of sudden conductive hearing loss following sneezing. Surgical exploration of the middle ear revealed a fragmented stapedial foot plate. Stapedectomy was performed with a satisfactory result.

Edison B, Holinger PH: Traumatic pharyngeal pseudodiverticulum in the newborn infant. *J Ped 82:483, 1973*

The recognition of post-traumatic hypopharyngeal diverticula has been a recent clinical observation in the newborn infant. Symptoms consist of excessive salivation, choking, and cyanosis. The diagnosis is suggested by fluoroscopy during swallowing of contrast material and confirmed by hypopharyngoscopy. The favorable outcome of the two infants reported suggests that conservative therapy with gavage or gastrostomy feedings should be considered. Blind passage of a nasogastric tube is hazardous and may make conditions worse instead of better; failure to recognize the nature of the lesion led to reinsertion of a nasogastric tube in one instance. Healing is usually fairly rapid within several days to a month. Cervical mediastinotomy or thoracotomy drainage may be necessary if there is wide extravasation of barium or if a complicating infection fails to respond to medical management.

Holinger PH, Jensik RJ: Halting the progress of Zenker's diverticula. *Geriatrics 28:133, 1973*

The pharyngoesophageal (Zenker's) diverticulum consists of a protrusion of mucosa through a weak point of the cricopharyngeus muscle; normally, the contraction and tone of this muscle presents a barrier to the swallowed bolus, which is propelled there by the strong muscles involved in the first stage of the swallowing mechanism. The insidious progression of symptoms is due to incoordination between the tongue, the constrictors of the pharynx and the cricopharyngeus. It is apparently a product of the process of aging, since most patients are beyond 60 years of age when the diagnosis is finally made. Treatment is surgical: inversion of the sac, single or two-stage diverticulectomy, or the more recently advocated diverticulotomy. In our own experience, single-stage diverticulectomy gives best and most permanent results for most patients, but endoscopic diverticulotomy is the preferred method in the debilitated older patient. Complications are not uncommon in this age group, increasing with procrastination and postponement of the corrective procedures.

Urology

Sullivan H, Gilchrist RK, Merricks JW: Ileocecal substitute bladder: Long-term followup. *J Urol 100:43, 1973*

Followup is reported on 40 patients who underwent ileocecal bladder construction. The basic points in surgical technique are discussed. Six patients are alive and their condition is evaluated. The 34 patients who died were investigated for continence of the new bladder, ureteral reflux and the status of renal function.

Sullivan H, Gilchrist RK, Merricks JW: Ileocecal substitute bladder: Long-term follow-up. *Yearbook of Urology, 1973, p. 158*

Follow-up of 21 male and 19 female patients having ileocecal bladder construction during 1949-63: Of these, 37 had malignancy with primary or secondary involvement of the bladder. Four patients underwent palliative diversion.

TECHNIC.—After appendectomy, the terminal ileum is divided about 5 in. proximal to the ileocecal valve and the right colon at least 8.5 in. distal to the valve. The new bladder is rotated so it lies transversely with the ileum pointing up and to the right. The right ureteroneocecostomy is done first, the ureter being implanted into a submucosal tunnel running crosswise to the long axis of the cecal pouch. The left side of the pouch is then pushed through an opening in the sigmoid mesentery. Usually splinting ureteral catheters are not placed.

The new bladder is sutured down to retroperitoneum, and the terminal ileum is placed so that it comes up in a straight line from the bladder through a skin stab wound near McBurney's point. A catheter is placed in the new bladder before the abdomen is closed.

Complete continence was gained by 94 percent of the patients. The average patient required catheterization every four to six hours during the day and perhaps once at night. Retrograde cecograms showed reflux in 3 of 38 patients studied. No renal calculi occurred. Three early patients had bladder calculi when nonabsorbable sutures used to close the outer coats for the new bladder worked inside, acting as a nidus. One patient with precystectomy pyeloureterectasis had serious infection requiring nephrectomy. One patient required temporary bilateral nephrostomy postoperatively for lower ureteral obstruction. No significant chemical imbalance developed in any patient. No deaths resulted from renal failure. Six patients are living 13 to 20 years postoperatively with functioning ileocecal bladders.

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ONCOGENIC VIRUSES OF PRIMATES: A REVIEW

Friedrich Deinhardt
Jean B. Deinhardt

ABSTRACT. The basic host-virus interrelationships of several tumors induced in nonhuman primates with C-type RNA and herpes-like DNA viruses have been established. Understanding of these relationships is important for the study of human tumors and the development of tumor therapy.

During the early 1960s it became clear that nonhuman primates would probably be needed as experimental animals in tumor virus research. With this objective in mind, the National Cancer Institute (National Institutes of Health, U. S. Public Health Service) began evaluating the usefulness of various species of nonhuman primates. Several species were evaluated for their general usefulness as laboratory animals, and especially for their susceptibility to viruses with known or potentially oncogenic properties. Similar studies were performed simultaneously in the USSR, and tumors induced by C-type RNA viruses in nonhuman primates were reported first by Zilber et al.[1,2] and Munroe, et al.[3] Both groups studied Rous sarcoma virus (RSV)-induced tumors in *Macaca mulatta, M. nemestrina* and *Papio hamadryas.* The susceptibility of the primates used in these studies usually depended on the use of immunosuppressive therapy but, even with immunosuppression, most tumors regressed spontaneously.

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In subsequent studies, Rous sarcoma virus was also shown to induce tumors in *M. mulatta* after intracerebral inoculation[4] and in *Saimiri sciureus, Galago crassicaudatus* and African green monkeys but again most tumors regressed spontaneously.[4-6] Another oncogenic C-type virus, feline fibrosarcoma virus (FeSV), induced tumors in *Saimiri sciureus,*[7] *M. radiata, M. mulatta* and *M fasicularis*[8] but these tumors, like the Rous sarcoma-induced tumors, regressed spontaneously. And Yaba virus, a simian DNA virus, induced histiocytomas in nonhuman primates under both natural and experimental conditions, and these tumors too usually regressed.[9-12]

In marked contrast to studies in which animals usually needed to be immunosuppressed and tumors usually regressed, some species of marmosets (*Saguinus* [*Oedipomidas*] *oedipus, S. nigricollis* and *S. fuscicollis*) are regularly susceptible to three C-type RNA tumor viruses[13-26] and to three or four oncogenic herpesviruses (for review see References Nos. 27 and 28). Progressive sarcomas were induced by Rous sarcoma virus in all marmosets inoculated before five months of age, and immunosuppression was unnecessary. Similar results were obtained with feline fibrosarcoma virus: virus strains which had induced tumors that later regressed in other primate species, induced progressive sarcomas in marmosets.[29] More recently, a C-type virus was isolated from a fibrosarcoma of a woolly monkey (simian sarcoma virus type 1 [*Lagothrix*], SSV-1) and this virus also induces fibrosarcomas in marmosets.[22,26]

Melendez et al.[30-33] isolated two antigenically distinct herpesviruses, *herpesvirus saimiri* and *herpesvirus ateles*, from squirrel and spider monkeys respectively, and these viruses cause no recognized disease in their natural hosts, although they regularly induce malignant lymphomas with or without leukemia when inoculated into a number of other New World nonhuman primates.[32-36] The first human virus, Epstein Barr virus (EBV) recently has been added to this category because it has been shown by at least four laboratories to induce lymphomas in marmosets.[37-40] and possibly also in an occasional owl monkey.[41]

To these agents, all oncogenic in nonhuman primates and particularly virulent in marmosets, which have been the principal interest of our laboratories for over ten years, must be added the viruses causing leukemias and/or lymphomas in *P. hamadryas* and *M. speciosa* inoculated with human leukemic materials (to be discussed by Professor Lapin), the oncogenic potential of cytomegaloviruses in primates reported by Dr. Deichman, and the viruses found in human tumor cells heard about from a number of speakers.[42-50] In addition, the viruses isolated from lymphomas of gibbons (*Hylobates lar*),[51-54] from a mammary tumor of a rhesus monkey[55-75] and the so-called endogenous C-type-RNA viruses recently isolated from placentae of several primate species (including man) and from normal primate tissues,[77-89] and the small DNA viruses such as polyoma, SV-40, and similar viruses isolated from nonhuman primates, and from patients with progressive multifocal leucoencephalopathy, or from patients under prolonged immunosuppression after transplantation; and adenoviruses should be added to the group of oncogenic viruses of primates. Papova- and adenoviruses induce tumors in lower mammals but not in primates; however papovaviruses transform some primate cells *in vitro*.

Whereas 10 years ago only RSV was known to induce tumors in primates, by today this list has become rather long. So an attempt will be made only to categorize the various agents which are oncogenic in primates and to point to some observations which may be important for future research.

The agents can be subdivided into 1) the C- or B- type RNA or oncornaviruses, 2) the large DNA viruses of which only the herpesviruses of this group are important at this time, and 3) the small DNA or papovaviruses (Table 1). Within each of these groups the viruses which are true primate viruses (i.e. their natural hosts are primates) can be separated from viruses of other species which can, at least under experimental conditions, induce tumors in non-human primates. So far, this distinction applies only to the oncornaviruses, as only primate herpesviruses have been associated with tumor induction in primates, a finding which may change in the future as more viruses from other genera are tested. There is one possible exception to this rule—the papova-like viruses isolated from man which will induce brain tumors in hamsters but have as yet not been shown to be oncogenic in primates.

Of the oncornaviruses, viruses from lower mammals as well as a virus (RSV) from another class of animals (*Aves*) have induced sarcomas in some nonhuman primate species, and among these some species of marmosets are the most susceptible. The number of viruses isolated from various nonhuman primates is rapidly growing but true oncogenic potential has been demonstrated only for the C-type virus isolated from a fibrosarcoma of a woolly monkey (SSV-1).[21] This virus induces slowly but progressively growing fibrosarcomas in some species of marmosets,[22-26] and small tumors, which however spontaneously regress, in some squirrel monkeys. SSV-1 causes true gliomas by intracerebral inoculation of marmosets;[93] these tumors are slowly progressing over several months; they produce virus, and it is interesting that the tumor-bearing animals develop much higher neutralizing serum antibody titers (up to 1:8000) than animals inoculated intramuscularly or intraperitoneally. SSV-1 has been studied in detail *in vitro* and has been shown to have

TABLE I

VIRUSES WITH ESTABLISHED OR POTENTIAL ONCOGENICITY IN PRIMATES

Type of virus	Cell Transformation		Genome Expression	
	in vivo	*in vitro*	*in vivo*	*in vitro*
PRIMATE VIRUSES				
Type C				
Simian sarcoma virus, type I *(Lagothrix)*	+	+	+	+
Simian sarcoma associated virus, type I *(Lagothrix)*	(−)	−	?	+
Gibbon ape lymphoma virus	(+)	−	(+)	+
Endogenous viruses of baboon, rhesus monkey and man	(−)	−	− or +	±
Type B or ϑ				
Mason-Pfizer monkey virus (MPMV) (from a rhesus monkey breast ca)	?	(±)	?	+
MPMV-like viruses from human tumor cell cultures	?	−	?	+
Herpesviruses				
Epstein-Barr-Virus	+	+	±	+
Herpesvirus saimiri	+	(−)	−	+
Herpesvirus ateles	+	+	−	+
Cytomegalovirus	(±)	(−)	+ or −	+
Herpesvirus simplex	?	+	+ or −	+
Other Viruses				
Yaba virus	+	(−)	+	+
Yakovleva—Lapin agent (not classified)	+	(−)	?	?
Adenovirus	−[1]	+[3]	+	+ or ±
Papovaviruses				
SV-40	?[1]	+	+ or −	+
BK	?[1]	+	+	+
JC	?[1]	?	+	+
NON-PRIMATE VIRUSES				
Type C				
Rous sarcoma virus (type D)	+	+	−	− or ±
Feline sarcoma virus	+	+	− or +	+
Mouse sarcoma virus	−[1]	+	−	(±)
Herpesviruses				
Marek's disease virus	−[2]	−	−	−
Papovaviruses				
Polyomavirus	−[1]	+	−	(±)

\+ = positive or full virus expression, antigens, complete infectious virus

± = probably positive but not conclusively proven, partial viral expression, formation of some antigens

− = negative or no detectable virus expression other than transformation in the case of transformed cells

() = insufficient data, needs confirmation

? = not known

[1] = induces tumors experimentally in lower mammals

[2] = induces tumors in chicken and full virus expression occurs in some chicken tissue *in vivo* and in susceptible chicken cells *in vitro*

[3] = transformation of cells of lower mammals only

all the characteristics of a typical C-type RNA sarcoma virus.[26,94] Like most others it appears to be defective[25,95] and has a nontransforming associated virus (simian sarcoma associated virus, SSAV-1).[25,26] SSAV-1 has been isolated in pure form, but attempts to obtain pure SSV-1 preparations free of SSAV-1 generally failed, with the exception of one recent report of isolation of clones of SSV-1 which can infect and transform cells without the presence of a helper virus.[96] Cells infected by this apparently competent SSV-1 produce small amounts of infectious SSV-1 (without SSAV-1) which contains the major proteins of SSV-1. As these experiments were performed in rat cells, however, one cannot completely rule out the possibility that the endogenous rat virus information in these cells provides some helper activity. The nucleic acids,[26,97-99] the RNA-dependent DNA polymerase[97,98] and the other structural viral proteins of SSV-1/SSAV-1 have been well characterized[100-104] Preliminary evidence for the presence of the SSV-1/SSAV-1 genome in normal primate cells was reported by Goodman et al.,[105] but this was disputed by another laboratory,[99] and is currently under further study. SSAV-1 can be titrated like other mammalian nontransforming leukemia viruses by evaluation of formation of syncytiae in an xc-cell mixed culture test.[104]

There is good but only epidemiological evidence that the so-called "gibbon ape lymphoma virus" (GAL) is associated with lymphomas in gibbon apes, but until now it has been impossible to show tumor induction by this virus in experimentally inoculated monkeys including gibbons, and the virus, although it will grow in a number of cell cultures, does not transform cells *in vitro*.[51-54,107] GAL and SSAV-1 although isolated from an Old World and New World monkey respectively are almost identical by antigenic analysis[54,100,102-104,107,108] by interference with SSV-1[109] and by molecular hybridization.[88,89,110] Minor antigenic differences between the two viruses have been demonstrated recently by quantitative differential micro-complement fixation tests[103] and by radioimmunoassays.[100] In addition, both SSV-1/SSAV-1 and GAL share partial nucleic acid homology with some murine C-type viruses, particularly Kirsten sarcoma virus,[88,110,111] but also with the DNA product of an endogenous RNA-dependent DNA polymerase reaction of "virus-like particles from fresh human acute leukemic blood cells."[111] These data have raised a number of questions about the origin of SSV-1/SSAV-1 and GAL, and the interrelationships between these viruses clearly need further study. Nevertheless use of DNA probes of these viruses in the search for human and other primate C-type viruses is clearly warranted.

The virus isolated from a mammary tumor of a rhesus monkey (Mason-Pfizer Monkey Virus, MPMV)[55-76] is morphologically distinct from C-type or B-type viruses but is similar to a number of viruses isolated from human tumor cell cultures,[42-50] and to viruses demonstrated in human milk.[60,112] MPMV has not induced tumors in inoculated animals, and has a limited ability to transform cells *in vitro* (a finding which needs further clarification by additional studies).[75] So the relationship of MPMV-like viruses to neoplasia is unclear but the presence of these agents in so many tumor cell cultures is interesting. These viruses share no antigenic relationships with C-type leukemia/sarcoma or endogenous C-type viruses and differ from the latter by molecular hybridization. Their antigenic relationships and nucleic acid homology to the classical B-type virus, mouse mammary tumor virus (MMTV), need further clarification.

The latest group of C-type RNA viruses, those isolated from placental and normal tissues of baboons, rhesus monkeys[77-89] and man, is antigenically and by molecular hybridization different from the other two C-type primate viruses (SSV-1 and GAL) and also from MPMV or the human MPMV-like isolates, but it shares some antigenic cross-reactivity and nucleic acid homology with the endogenous feline C-type viruses (RD-114/CCC).[88] The genomes of these endogenous viruses seem to be carried to a much larger extent in nor-

mal cells (possibly all cells of a given species carry the genome of the corresponding endogenous virus)[87,89] than the genomes of true leukemia and sarcoma viruses.[99,105] The biological function of these viruses is unknown but it is tempting to speculate that they have regulatory functions, particularly during the period of rapid cell proliferation in embryonal development.

The virology and immunology of tumors induced by C-type viruses in primates merit some attention. Virus expression in the tumors ranges from an almost completely repressed state in RSV-induced tumors to full virus expression in SSV-1 induced tumors. Tumors induced by RSV usually contain no or only minimal amounts of viral antigens but RSV-induced tumors have virus specified, cell surface antigens; virus can be rescued by co-cultivation with chick embryo cells and the viral genome has been demonstrated in all tumors by molecular hybridization techniques.[105,113] Similarly tumors induced by FeSV derived directly from cat tissues express the virus genome to only a limited extent, but derepression and complete expression of all viral functions occurs if FeSV-induced marmoset tumors are grown in cell culture or if FeSV is passed from marmoset to marmoset.[29] Finally, SSV-1 is completely expressed in primary tumors as well as in tumors induced with SSV-1 grown serially in marmoset cells.[22,26] Antibodies to the viral antigens are produced only poorly in animals carrying RSV-induced tumors but reach average titers in animals carrying FeSV or SSV-1-induced tumors, and the excessively high titers of neutralizing antibodies produced by animals with SSV-1 induced brain tumors (gliomas) are particularly interesting. Cytotoxic antibodies, blocking antibodies and lymphocytotoxicity against various tumor cells have been studied recently and showed that the virus-transformed tumor cells probably carry at least two altered cell surface antigens, one virus specific antigen and one common at least to RSV and FeSV transformed cells.[114,115] Abrogation of the cell-mediated responses is possible by immunosuppression, particularly with a specific, purified anti-marmoset lymphocyte globulin, and this results in more rapid tumor progression.[116] Ideally these tests are performed by obtaining skin and muscle biopsies from individual animals and transforming the cells *in vitro* with various viruses[116] (RSV, FeSV, SSV-1, polyoma, SV-40 and BK, a human papova-virus-like isolate) (Fig. 1). Such an experimental design, comparing cell lines transformed by different viruses in an autochthonous system, avoids interference caused by transplantation antigens. One transformed line is inoculated back into the same animal from which the original biopsy was obtained; the immune responses of the animal directed towards the transformed cells used for the inoculation, as well as to the cells transformed by other RNA or DNA viruses, can be observed. In general, marmosets are most susceptible to tumor induction by oncogenic C-type viruses during the first few months of life and become, with some exceptions, almost completely resistant to tumor induction during adulthood, but appear to regain susceptibility when they reach old age.

In contrast to C-type RNA virus-induced sarcomas, marmosets and animals of other susceptible nonhuman primate species of all ages succumb to inoculation of as few as 10 plaque-forming units of *herpesvirus saimiri* (HVS) or *herpesvirus ateles* (HVA)[30-36,117] by the development of lymphomas and/or leukemias. HVS occurs naturally in squirrel and HVA in spider monkeys without producing a known disease in their natural hosts, but if HVS or HVA is transferred to some other nonhuman primate species, all or most inoculated animals develop lymphomas and/or leukemias[27,28,118-124] (Table II). HVS and HVA share many characteristics with EBV, a similarity which has provided additional, indirect evidence for a causal relationship between EBV and Burkitt's lymphoma (Table III). In addition three strains of EBV (B95, Kaplan and EB-3) have recently been shown to cause lymphomas in experimentally infected marmosets[28,37-40] and possibly also in an occa-

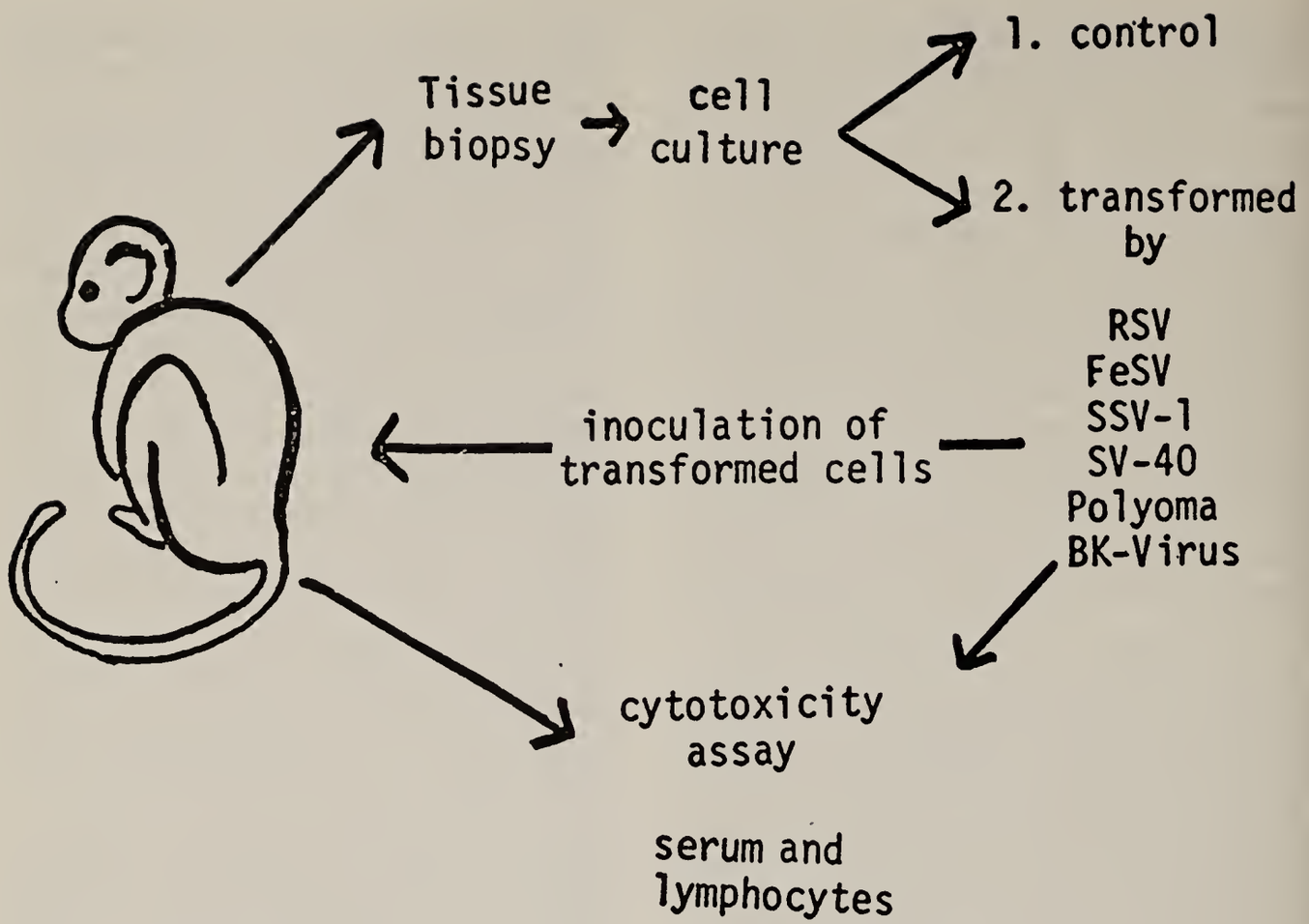

Fig. 1—Protocol for cytotoxicity assay of altered cell membrane antigens

sional owl monkey,[41] a direct proof of the oncogenicity of EBV *in vivo*. Host cell-virus interrelationships are similar in EBV and HVS or HVA i.e., all three are transmitted horizontally, they transform lymphocytic cells *in vivo*, but most other virus genome expressions are repressed. However, if the transformed cells are grown *in vitro*, virus genome derepression occurs spontaneously.[125,126] Distinct "early" and "late" viral antigens and cell membrane antigens have been identified in all three systems;[28,123,127–130] in general the antibody responses to these antigens are similar,

TABLE II

HOST RANGE OF SIMIAN ONCOGENIC HERPESVIRUSES

	Natural Host	Experimental Hosts
Herpesvirus saimiri	Squirrel monkey *(Salmiri sciureus)*	*Marmosets *(Saguinus* sp.*)* *Owl monkeys *(Aotus trivirgatus)* *Cinnamon ringtail monkey *(Cebus albifrons)* *Spider monkey *(Ateles* sp.*)*
Herpesvirus ateles	Spider monkey *(Ateles* sp.*)*	*Marmosets *(Saguinus* sp.*)* *Owl monkeys *(Aotus trivirgatus)*

*Respond with lymphoma and/or leukemia

and a life-long carrier state follows primary infection. Antigens similar to the most recently described nuclear antigen of EBV-transformed cells (EBNA)[131] have not yet been identified in HVS or HVA-infected cells. It is puzzling however why HVS or HVA does not induce malignant disease in their natural hosts although they do induce lymphomas and/or leukemias regularly in certain experimental primate species. But if HVS and HVA produce lymphomas in their natural hosts with the same frequency that EBV induces lymphomas in man, such cases probably would not yet have been identified, as the numbers of squirrel or spider monkeys studied have been too small. As an explanation of the absolute oncogenicity of HVS and HVA in some experimental hosts, in comparison to the non-existent or low pathogenicity in their natural hosts, one should consider the possibility that virus genome integration in the experimental animal species occurs in such a way that cell transformation results, whereas in the natural host viral genome integration occurs in a silent region, but there is no experimental data to support or refute such a hypothesis. Another explanation could be that cell transformation occurs with equal frequency, both in natural and experimental hosts, but transformed

TABLE III

COMPARISON OF EBV WITH HVS AND HVA*

	EBV	HVS/HVA
Biological		
Primary infection	Infectious mononucleosis	Unknown
"Secondary" disease	Burkitt's lymphoma Nasopharyngeal carcinoma	Unknown
Experimental host	Lymphoma	Lymphoma, leukemia
Transmission	Horizontal	Horizontal
Carrier state	Lifelong	Lifelong
Type of transformed cells	B-cell	T-cell
Virus genome expression		
Cell transformation		
in vivo	Yes	Yes
in vitro	Yes	HVS: No HVA: Yes
Virions		
in vivo	No	No
in vitro	Yes	Yes
Early and late antigens		
in vivo	No	No
in vitro	Yes	Yes
Nuclear antigens (EBNA)		
in vivo	Yes	?
in vitro	Yes	?
Cell membrane antigens		
in vivo	(Yes)	(Yes)
in vitro	Yes	Yes
Viral genome present:		
"normal" lymphocytes of carriers	Yes	Yes
tumor cells	Yes	Yes
Antibody production		
Primary infection:		
early antigen	Temporary	Temporary
late antigen	Persistent	Persistent
EBNA	Persistent	?
"Secondary disease":		
early antigen	Rising	Unknown
late antigen	Rising or persistent	Unknown
EBNA	Yes	Unknown
Malignant disease in experimental host:		
early antigen	Rising	Rising
late antigen	Rising	Rising or Persisting
EBNA	Yes	?

*Not all of the parameters have as yet been established

cells are immediately eliminated in the natural host and further virus spread, if any occurs, is limited by a strong immune response to viral antigens. Certainly squirrel monkeys form antibodies to HVS much more efficiently than experimental animals such as owl and marmoset monkeys, which almost always react to inoculation of HVS with the development of lymphomas and/or leukemias.[28] In contrast to EBV-transformed cells of man or monkeys, all of which have B-cell characteristics, the lymphocytic cells of experimental animals transformed by HVS or HVA all have T-cell characteristics.[28,132-135] Even lymphocytic cells from the same animal, transformed *in vitro* either by HVA or EBV, are T- or B-cell-like respectively and this seemingly specific tropism of EBV *vs* HVS and HVA for B- or T-cells is puzzling and not understood.[136] It will be important to see whether HVS or HVA occasionally induce neoplasia in their natural hosts, perhaps after treatment with chronic lymphoreticular stimulation, i.e., malaria, or after immunosuppression, and if the malignant cells in such disease are B- or T-cell-like.

SUMMARY

Several points are important. First: the basic host-virus interrelationships of several tumors induced in nonhuman primates with C-type RNA and with herpes-like DNA viruses have been established. These tumors should be used in future for chemotherapy[137,138] immunotherapy and vaccine studies. Second, the demonstration of endogenous C-type and of MMTV-like viruses in primates including man, makes nonhuman primates the ideal choice for studies on the pathogenic potential of these agents, because such experimental studies could not be done with human viruses in man. The antigenic and nucleic acid differences between the true oncogenic primate viruses (SSV-1 and GAL(?)) and the endogenous viruses, and their similarities to similar viruses from different animal species (i.e., SSV-1/SSAV-1 is related to MuLV/MUSV, and the endogenous primate viruses to the endogenous feline viruses, RD-114,CCC) are puzzling, and there is no satisfactory explanation for these interrelationships as yet. Horizontal transmission between species at some time in the species' evolutionary past with a simultaneous loss of infectivity by mutation, deletion or recombination with genetic information of the new host, has been suggested, but available data do not allow us to draw any conclusions.

Third, the lymphomas and leukemias induced by HVS and HVA, and the transmission with tumor induction of EBV to nonhuman primates has provided, probably for the first time, definitive proof for the oncogenicity of a human virus in primates. Indirectly such transmission also confirmed the conclusion, reached previously from indirect evidence, that EBV causes some lymphomas and possibly also nasopharyngeal carcinomas. Other pathogenetic mechanisms however have been considered, and it has been postulated that: (1) EBV induces tumors only indirectly by activating C-type RNA viruses, (2) transformation of cells by C-type RNA viruses activates EBV which then would only be a passenger virus, or (3) EBV and C-type RNA viruses act in some form as cocarcinogens.[139] In addition, a RNA dependent DNA polymerase was described in a HVS transformed lymphoblastoid cell line, and this has been considered as possible evidence that RNA tumor viruses may play some role in HVS or HVA induced lymphomas and/or leukemias in nonhuman primates.[140] These findings were, however, not confirmed in studies with different HVS induced tumors or tumor cell lines,[141] and tumor induction could be prevented by neutralizing HVS with monospecific antisera in the inocula.[142] It therefore appears more likely that EBV, HVS and HVA are indeed the primary cause of the neoplastic diseases they are associated with, and the activity of C-type RNA viruses represents nonspecific activation of endogenous virus which probably plays no role in tumor induction in these systems.

Fourth, the recent successful transformation of cultured primate cells, including man's, by HVA provides the possibility of establishing lymphoblastoid cell lines derived from isolated B- or T-cell clones by infection and transformation *in vitro* with EBV or HVA. This makes a dream of the immunologists come true, and it may provide an important side benefit in studies of basic immunology.

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THE CONSEQUENCES OF RIGHT VENTRICULAR STRESS UPON LEFT VENTRICULAR FUNCTION

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ABSTRACT. Considerable interest has evolved concerning the influence of primary right ventricular stress upon changes in left ventricular function. This interest was initially based upon findings of left ventricular hypertrophy in necropsy evaluation of patients with chronic obstructive lung disease. Many of these patients had no clinical or pathologic evidence for coronary, valvular or hypertensive heart disease.

Secondary left ventricular function changes have been clinically assessed in patients with pressure or volume overload of the right ventricle. Models for right ventricular pressure overload have been patients with chronic obstructive lung disease and associated cor pulmonale. Right ventricular volume overload and its effect on the left ventricle have been studied in patients with atrial septal defect. Left ventricular dysfunction has been defined in some studies as change in left ventricular end-diastolic pressure, stroke volume, or maximal velocity of contractile element shortening (V_{MAX}). In other studies, experimental volume or pressure loading of the right ventricle has demonstrated shifts of the left ventricular pressure-volume curve without significant abnormalities of left ventricular function, as determined by ejection fraction, or contractile state.

In experimental animals, biochemical abnormalities have been noted in both ventricles when one ventricle is primarily stressed. These abnormalities have included biventricular decreases in catecholamine and myofibrillar ATPase and increases in RNA and protein synthesis. In situations of primary stress on the right ventricle, some abnormality of left ventricular function may develop, as demonstrated by isolated length-tension studies.

Although there is considerable evidence for some modification of left ventricular performance after primary right ventricular stress, such as changes in pressure-volume curve of the left ventricle, there have been no correlations of left ventricular performance changes with extent of right ventricular disease.

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INTRODUCTION

Several large series of necropsy studies of patients with chronic cor pulmonale showed evidence for left ventricular hypertrophy, even without previous clinical evidence for hypertension, valvular or coronary artery disease. This led to speculation that right ventricular abnormalities may be associated with secondary alterations of left ventricular anatomy and function.

This possibility was further suggested by more recent studies demonstrating that biochemical changes may occur in both ventricles when one ventricle is primarily stressed.

Over the past decade these intriguing findings have stimulated assessment of the functional changes of the left ventricle in disease primarily involving right ventricular pressure and/or volume overload. Right ventricular hypertrophy, secondary to chronic obstructive lung disease or high-altitude hypoxia, has been the usual model for pressure overload investigations, and ostium secundum atrial septal defects the model for volume overload studies.

Some experimental studies have focused on the effects of pulmonary artery banding on abnormalities of the left ventricle, by measuring the increase in mass and incorporation of protein. Necropsy studies have utilized post-mortem volume overload of the right ventricle to determine effects on compliance and pressure-volume changes of the left ventricle.

The review of these studies will focus on the development of the concept of changes in left ventricular function resulting from right ventricular disease.

PATHOLOGY OF THE LEFT VENTRICLE IN RIGHT VENTRICULAR STRESS

Beginning in the 1930's, several autopsy and clinical studies of the hearts of patients with chronic cor pulmonale showed evidence of left ventricular hypertrophy.[1-10] Most patients were in the middle and older age groups. One study, by Scott and Garvin,[3] showed that 60 percent of these patients had a thickened left ventricular wall, unassociated with aortic valve lesions or coronary artery disease. Systemic hypertension was ruled out on the basis of previous clinical records. It was considered that left ventricular enlargement was due to hypoxia secondary to pulmonary disease. Others[11,12] have failed to demonstrate evidence of left ventricular abnormalities in patients with chronic cor pulmonale.

Aside from the possibility of hypoxia leading to left ventricular dysfunction, theoretical explanations for evidence of left ventricular hypertrophy have included: (1) expanded bronchial circulation, producing left ventricular volume overload and (2) mechanical interference with left ventricular performance by the hypertrophied right ventricle.[13]

Some studies appear to refute these explanations. For example, bronchiectasis and cystic fibrosis, conditions manifesting extensive bronchial collateral circulation and often considerable right ventricular enlargement, do not appear to be associated with left ventricular abnormality.[14] As for the influence of hypoxia on left ventricular enlargement, high altitude pulmonary hypertension rarely appears to produce this effect except in exceedingly severe hypoxic and polycythemic conditions.[15]

CLINICAL INVESTIGATION OF THE EFFECT OF RIGHT VENTRICULAR PRESSURE OVERLOAD ON THE LEFT VENTRICLE

Clinical assessment of left ventricular performance in chronic cor pulmonale has focused on patients with chronic obstructive airway disease and high altitude acclimatization, both associated with variable degrees of right ventricular hypertrophy secondary to pulmonary hypertension.

Left ventricular performance change has been variously defined in these investigations by the following clinical manifestations or measurements: (1) pulmonary congestion; (2) elevated left ventricular end-diastolic pressure (LVEDP) or pulmonary wedge pressure (PWP); (3) changes in stroke volume and ejection fraction, or evidence of dyssynergy of the left ventricle; and (4) changes of left ventricular contractility as measured by rate of rise of left ventricular pressure (dp/dt), maximal velocity of contractile element shortening (VMAX), and stroke work index. Efforts have been made to correlate these various criteria of left ventricular performance change with quantitative assessment of right ventricular abnormality. The use of these measurements of left ventricular performance will first be critically evaluated.

Pulmonary Congestion

Pulmonary congestion is frequently associated with left ventricular dysfunction. Several reports have suggested increased pulmonary extravascular volume in chronic obstructive pulmonary disease.[16,17] Rao, *et al.*[17] studied patients with chronic respiratory failure secondary to chronic obstructive lung disease and found, upon X-ray, that the left ventricle was enlarged. Other findings included left atrial enlargement and Kerley's *B* lines. Autopsy evidence of biventricular hypertrophy, dilatation, and pulmonary edema was present in several.

Other studies show inconclusive evidence of left ventricular failure associated with pulmonary congestion. McCredie[18] studied pulmonary extravascular fluid volume, using a double isotope dilution technique. Patients with chronic obstructive pulmonary disease and a history of prior congestive heart failure had a higher mean pulmonary extravascular volume than those without such history, correlating with an increased mean left atrial pressure. However, in only a few of these patients was this pressure above normal values. Normal PWP has been found in high altitude pulmonary edema, where severe pulmonary hypertension is evident.[19] Thus, the development of pulmonary edema *per se* does not necessarily involve increases in left-sided pressure.

It has been postulated that pulmonary edema in parenchymal lung disease may be a result of compliance alterations in the pulmonary vascular bed itself leading to increased pulmonary capillary pressure with only slight rises in pulmonary venous pressure.[20] One possible explanation for such pulmonary compliance abnormalities is restriction of pulmonary lymphatics leading to compromise of the pulmonary capillary removal mechanism producing an accumulation of fluid.[21]

Clinical pulmonary congestion does not necessarily reflect left ventricular performance changes, and may indicate abnormalities within the confines of the pulmonary circulation alone.

Changes in Pulmonary Wedge Pressure and Left Ventricular End-diastolic Pressure

PWP is considered to reflect mean left atrial pressure. However, some studies indicate that PWP may not reflect left atrial pressure in pulmonary disease.[22,23] Elevated resting LVEDP or PWP was found in several patients in Rao's series.[17] Burrows, *et al.*,[24] however, studied 50 patients with chronic airway obstruction over a seven-year period and demonstrated that PWP was normal at rest in all, and increased more than 8 mm Hg with exercise in only two of 25 patients. Studies of left ventricular pressure show that chronic obstructive pulmonary disease may be associated with increases in left ventricular end-diastolic pressure.[13,17,25] Baum, *et al.*[13] found an elevated LVEDP in almost 50 percent of his series.

Others have shown no increase in LVEDP. Davies and Ovary, unlike Burrows and his group, demonstrated that elevated LVEDP was not observed in COPD.[26] There is considerable evidence that even LVEDP may be an unreliable

index of primary left ventricular performance change and may be influenced not only by intrinsic left ventricular functional state but also by changes in intrathoracic pressure and central blood volume.[27,28]

Thus, PWP and LVEDP may not necessarily be considered good evaluators of left ventricular dysfunction *per se* in the setting of chronic cor pulmonale.

Assessment of Left Ventricular Performance Determined Angiographically

Various changes in left ventricular function have been observed in patients with chronic cor pulmonale. Frank, *et al.*[29] found a decreased cardiac index, stroke volume, left ventricular stroke work and ejection fraction in a series of patients with chronic cor pulmonale, when compared to normal subjects. End-diastolic left ventricular volume was found to be increased. Intrinsic left ventricular disease was excluded by absence of abnormal coronary artery perfusion or myocardial oxidative metabolism. There is evidence that these parameters of left ventricular function can decrease in older age groups without specific left ventricular pathology.[30]

Baum, et al.[13] demonstrated increased left ventricular wall thickness and/or end-diastolic chamber size in nine of ten patients evaluated with chronic obstructive lung disease. Left ventricular performance, as determined angiographically, demonstrated diminished ejection fraction with or without dyssynergy, in three of eight patients. There was, however, significant coronary artery disease in few of these patients, and therefore an ischemic process of the left ventricle could be in part responsible for these changes. As for left ventricular hypertrophy, the presence of this finding does not necessarily indicate depressed myocardial performance.[31–35]

Fishman[36] has pointed out that the finding of left ventricular hypertrophy may be due to a combination of severe hypoxia, electrolyte abnormalities and variations in the distribution of intramyocardial blood flow, aside from possible underlying coronary artery disease.

Hypoxia may affect left ventricular function, causing a direct depressant effect.[37] Decreased lactate extraction[38] and decrease in high energy phosphate compounds[39] also have been noted in the hypoxic heart. Other reports indicate that anoxia *per se* may not explain failure of the myocardium in the clinical setting of chronic obstructive lung disease.[40]

Analysis of left ventricular performance during changing activity has shown variable results in chronic obstructive lung disease. Left ventricular function curves determined by response of stroke work index/LVEDP to graded angiotensin infusions were shown to be abnormal in 14 of 15 patients with chronic obstructive lung disease.[13] Williams, et al.,[41] however, failed to demonstrate abnormality in stroke work index/LVEDP response to increased afterload, or a correlation between pulmonary hypertension with or without right heart failure and response of the left ventricle to increased afterload. In patients with chronic obstructive lung disease subjected to exercise, in another study, cardiac index increase was normal, and paralleled the increase in O_2 consumption.[24] By these criteria, left ventricular performance may be abnormal, but the significance of these findings is unresolved.

No correlation was found by Baum, *et al.*[13] between left ventricular dysfunction measured by diminished ejection fraction, elevated left ventricular end-diastolic pressure or angiographic rate of change of area of the left ventricle during systole, on the one hand, and the right ventricular end-diastolic pressure, on the other. The only correlation between left-sided function and pulmonary disease was a direct one between $PaCO_2$ and LVEDP.

Summarizing, clinical evaluation of left ventricular function in chronic right-sided pressure overload states has demonstrated variable decrease in left ventricular performance. There is no correlation of left ventricular dysfunction, when found, with the degree of right ventricular dysfunction. No direct evidence has been

demonstrated that the hypoxia of chronic obstructive lung disease causes abnormal metabolic function in the left ventricle, except possibly acidosis secondary to hypercapnia.

CLINICAL INVESTIGATION OF THE LEFT VENTRICLE IN RIGHT VENTRICULAR VOLUME OVERLOAD STATES (ATRIAL SEPTAL DEFECT)

The hypothesis that hypertrophy and dilatation of one ventricle could affect the performance of the other was first suggested by Bernheim in 1910.[42] He postulated that left ventricular dilatation could cause elevated right ventricular pressures by shifting the ventricular septum to the right, compressing the outflow tract of the right ventricle. It has been suggested by Kelly, *et al.*[43] that a reversed Bernheim effect could cause left ventricular performance changes in right ventricular volume overload.

Studies of the behavior of the left ventricle in conditions of right ventricular volume overload have involved patients with secundum atrial septal defects. This condition, in its isolated form, should presumably not be associated with abnormalities of left ventricular performance except as affected by either changes in inflow from the left atrium or changes in the common ventricular septum.

In order to place assessment of ventricular performance in perspective in atrial septal defect, we will first review some hemodynamic findings in this condition. In general, the performance of the left ventricle results from the end-diastolic volume changes, which are in turn partly determined by left atrial inflow. In secundum atrial septal defect, preferential flow from the left atrium to the right atrium is related to atrial pressure gradient differential and differences in right and left ventricular compliances. Dexter[44] concluded on the basis of his hemodynamic evaluations that preferential flow from left to right resulted not only from atrial pressure gradients but from differences in ventricular compliance.

Recent studies demonstrate a divergence of left and right atrial pressures in atrial septal defect and that there indeed may be a gradient between the atria.[45–47]

Several studies have shown left ventricular dysfunction in both adults and children with atrial septal defect. Levin, et al,[48] demonstrated decreased left ventricular stroke work index and ejection fraction in children with secundum atrial septal defect with greater than 50 percent left-to-right shunt. None of these children was in clinical left or right heart failure. Cardiac index was low, and left ventricular end-diastolic pressure was normal. Even in infancy, atrial septal defect with greater than 50 percent shunt has produced angiographic evidence of left ventricular dysfunction in symptomatic patients.[49]

In adults with atrial septal defect, Popio, et al.[50] demonstrated, by angiographic determination, reduced left ventricular volume, stroke volume, and cardiac index. Flamm, et al.[51] demonstrated, in adults, a low resting left ventricular output associated with a very low normal left ventricular end-diastolic pressure. During exercise, in patients with severe right ventricular failure, the systemic cardiac output showed a less than optimal increase in relation to increase in oxygen consumption. This response was not found in situations where right ventricular failure was absent.[51]

Saksena, *et al.*,[52] studying adults with atrial septal defect, found evidence of left ventricular dysfunction in 17 of 24 on the basis of decreased left ventricular minute work/tension time index ratio, decreased peak left ventricular dp/dt, decreased left ventricular stroke index/systolic ejection period ratio (systolic ejection rate) or increased LVEDP.

In another series of 35 adults with atrial septal defect, mean LVEDP was significantly *lower* than that of normal controls.[53] Left ventricular systolic output was decreased and, in some, left ventricular end-diastolic volume was *diminished.* No correlation was found between left ventricular end-diastolic volume and right

ventricular end-diastolic pressure.

The findings of Flamm, *et al.*[51] suggest a possible generalized myocardial response to overload of one ventricle which produces functional and structural impairment of the other ventricle. Saksena's group[53] demonstrated, however, that a closure of the atrial septal defect did not produce early improvement in left ventricular dysfunction despite reduction in the right ventricular load. This suggests that mechanical overload may produce permanent intrinsic abnormalities of the other ventricle.

One study of isolated right ventricular overload, due to either pressure or volume loading, demonstrated decreased left ventricular VMAX in the patients with right ventricular overload, compared with normal patients, although LVEDP and ejection fraction were normal.[54]

Non-invasive studies using ultrasound have demonstrated abnormal systolic motion of the intraventricular septum in atrial septal defect.[55] In studies of dogs with induced right ventricular volume overload, abnormal intraventricular septal motion was noted in systole.[56] In studies of patients before and after repair of atrial septal defect, the abnormal intraventricular septal motion found in 75 percent before operation returned to normal in only one.[56] Right ventricular volume overload did not necessarily produce this effect, however, since patients with ventricular septal defect had normal intraventricular septal motion.

The reasons that intraventricular septal abnormalities persist after surgery for atrial septal defect are speculative. Persistent compliance abnormalities associated with the chronic volume overload may be a possible cause.[57,58]

These studies of atrial septal defect demonstrate that with volume overload of the right ventricle, left ventricular function may be altered. The finding of changes in VMAX with normal hemodynamic studies suggests an altered state of contractility of the left ventricle which may be secondary to a generalized myocardial response to overloading of one ventricle.

THE EXPERIMENTAL MODEL: EFFECT OF HEMODYNAMIC CHANGES OF RIGHT VENTRICLE ON PRESSURE-VOLUME CHANGES IN THE LEFT VENTRICLE

The right and left ventricles of the mammalian heart are anatomically related by a common septum and by spiral fiber bundles. It might be expected that filling one ventricle would affect the distensibility of the opposite chamber.

Experimental observations have attempted to define such pressure-volume changes under conditions where either or both ventricles are variably stressed.

The two ventricles fill to approximately equal volume at different pressures when the septa are intact, the right ventricle being more distensible.[59] Taylor, et al.[60] studied the effect of right ventricular distensibility on changes in left ventricular pressure-volume relations, in both the intact and isolated dog heart. It was found that the magnitude of influence of filling one ventricle on the filling of the other was minimal at the usual physiologic levels. As LVEDP increased to 20 mm Hg, however, right ventricular abnormalities had considerable effect on decreasing left ventricular distensibility. At lower left ventricular pressures, volume overload of the right ventricle did not affect left ventricular volume changes, but at higher left ventricular pressure increased right ventricular volume diminished the left ventricular compliance. This was assumed to be related to the common septum and bundles.

Urschel, *et al.*[61] investigated the effect of incremental increase in right ventricular pressures on left ventricular function in isolated supported canine hearts. Increasing right ventricular end-diastolic pressure by 10 mm Hg caused an increased left ventricular end-diastolic pressure of 6 mm Hg. These changes were associated with changes in left ventricular and right ventricular geometry. Left ventricular cardiac output, heart-rate and afterload were kept constant by the experimental conditions.

Thus, right ventricular filling may have some effect on left ventricular geometry as well as on left ventricular filling pressure.

Kelly, *et al.*[43] studied left ventricular performance after chronic right ventricular pressure and volume loading in dogs. Left ventricular function was appreciably depressed, with decreased peak left ventricular pressure, wall stress and dp/dt, with LVEDPs of from 1 to 20 mm Hg. Measurements were made during isovolumic left ventricular contractions. In the potassium-arrested heart, previously subjected to chronic right ventricular loading, left ventricular pressure-volume relations changed from control hearts. A specific left ventricular volume increase was associated with a higher left ventricular filling pressure than in control hearts. In these studies, when peak left ventricular pressure and wall stress were compared with left ventricular end-diastolic volume rather than left ventricular end-diastolic pressure, there were no differences from normal controls. Peak left ventricular dp/dt and VMAX did remain depressed, however. Therefore, left ventricular contractility may indeed decrease. Of note was the decrease in myocardial norepinephrine concentrations in both ventricles after chronic right ventricular overloading. In post-mortem studies, left ventricular pressure-volume curve was normal when the right ventricle was empty, indicating that the intrinsic compliance of the left ventricle was not altered and that changes observed in the left ventricular pressure-volume curve during various right ventricular rhythm changes were due solely to effects of changes in the right ventricular volume.

Other studies of compliance changes in the post-mortem hearts of healthy dogs showed that pressure-volume relations of each chamber were highly dependent upon filling of the contralateral chamber.[58] Volumes accepted by the cardiac ventricles during a simultaneous biventricular infusion were significantly less than volumes determined with infusion into one ventricle alone.

An experimental model for right ventricular pressure overload is brisket disease of cattle. In this condition, left ventricular end-diastolic pressure was found to be elevated with right heart failure associated with severe pulmonary hypertension.[63] Left ventricular filling pressure returned to normal with reversal of this process.

These experimental studies and observations suggest that geometric configurational changes can occur in the left ventricle with right ventricular volume overload. These changes may be associated with alteration of the pressure-volume curve of the left ventricle. If left ventricular function is compared with left ventricular end-diastolic volume rather than to left ventricular pressure, left ventricular dysfunction is minimal. Even so, there is indication for some decreased left ventricular contractility with right ventricular overload, as measured by VMAX and peak left ventricular dp/dt.

BIVENTRICULAR BIOCHEMICAL CHANGES ASSOCIATED WITH ISOLATED OVERLOAD OF ONE CHAMBER

There is considerable evidence that stress involving one ventricle can lead to biochemical abnormalities in both. In the case of failure of one ventricle, decrease in levels of catecholamines and ATPase activity, and variations in rates of protein sythesis have been found in both ventricles.

Studies of experimental right heart failure in animals have shown that failure is associated with a reversible change in adrenergic neuro-transmitter and decreased norepinephrine stores in both ventricles.[64,65] It might be suggested that these decreases in norepinephrine stores may affect left ventricular contractility. Uptake and binding of norepinephrine under these circumstances appear not to be affected, however.[66] Since plasma norepinephrine is readily available for uptake, it is unlikely that these depleted tissue levels in non-stressed left venticular myocar-

dium would explain decreased contractility occasionally found in right ventricular stress.

After pulmonary artery binding, myofibrillar adenosine triphosphatase is decreased in both right and left ventricles.[66] There is associated decrease in contractility, expressed as maximum rate of force development at the peak of the length-tension curve, related to decreased myofibrillar ATPase. Other studies also have indicated left ventricular biochemical abnormalities in right ventricular failure.[67,68]

Ventricular compliance may be affected by changes in connective tissue. Buccino, *et al.*[69] demonstrated an increased concentration of hydroxyproline in both right and left ventricles when pulmonary artery was banded experimentally. Hydroxyproline is found only in collagen, and therefore this might indicate an increase in connective tissue elements in the left ventricle. There was no evidence that decreased coronary blood flow or hypoxia could account for this change. On the other hand, collagen distribution is greater in the epicardial than endocardial region, paralleling the distribution of vascular elements. No explanation is apparent for this left ventricular response to right ventricular stress.

There is evidence that a hypertrophic response may be obtained in both ventricles with pressure overload of only one. Gluck, *et al.*[70] found that RNA concentration increased in both ventricles with right ventricular banding. Myocardial protein synthesis also increases in the unstressed left ventricle.[71] There is much speculation over what causes the stimulus for RNA and protein synthesis induced by stress. It is possible that cardiac contractile action changes[72] and relative hypoxia[73] may induce the stimulus to myocardial cell growth and possibly hypertrophy.

These findings may partially explain the development of left ventricular hypertrophy in patients with primary right ventricular stress, as in cor pulmonale.

CONCLUSION

Clinical and experimental studies of left ventricular performance after right ventricular stress have demonstrated variable changes in left ventricular function. These investigations have stimulated considerable interest in the interrelationship of physiologic and biochemical processes between the two ventricular chambers of the heart.

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THE ENIGMA OF PRIMARY PULMONARY HYPERTENSION

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ABSTRACT. Primary pulmonary (arterial) hypertension is a diagnosis of exclusion, and may be difficult to confirm even at autopsy. One may fairly accurately infer the diagnosis by considering the patient's clinical course along with results of cardiac catheterization. Cardiac catheterization also may be of prognostic importance. In the adult population the disease is predominant in females, and mean survival time after onset of symptoms has been reported to be 2.5 years, with a few patients surviving longer than a decade. Clinical manifestations are those of severe pulmonary hypertension of any etiology. Congenital as well as acquired forms of the disease possibly exist.

INTRODUCTION

In recent years, considerable investigation has been directed to the evaluation of pulmonary circulatory dynamics. For both congenital and acquired heart disease, the severity and reversibility of pulmonary hypertension may be governing factors in the decision for cardiac surgery. Cardiac catheterization plays an integral role in determining the etiology of pulmonary hypertension.

At least three pathophysiologic mechanisms of pulmonary hypertension exist: (1) pulmonary venous hypertension; (2) increased pulmonary blood flow (hyperkinetic hypertension); and (3) reduction of cross-sectional area of the pulmonary vascular bed due to reactive constriction or vascular obliteration. These mechanisms are not always clearly separable and may, in fact, coexist. In each of these conditions the pulmonary artery pressure is raised, but for quite different physiologic reasons. In pulmonary hypertension, pulmonary artery pressure elevation is mostly passive and the vascular resistance is normal or moderately elevated. An example of this type is mitral valvular disease. In hyperkinetic pulmonary circulatory states, pulmonary arterial pressure elevation is secondary to an excessive pulmonary blood flow and pulmonary vascular resistance is normal or slightly elevated. An example of this type is atrial septal defect. Should a patient with atrial septal defect develop the Eisenmenger syndrome, the shunt may become reversed because of markedly elevated pulmonary vascular resistance. In reactive or obliterative pulmonary arterial hypertension, the pulmonary vascular resistance may approach or exceed systemic vascular resistance. Examples of this type are chronic hypoventilation, severe chronic bronchitis-emphysema, recurrent pulmonary thromboembolism, and conditions of unidentifiable etiology which are accordingly labelled as idiopathic or primary pulmonary (arterial) hypertension.

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Two patients who were diagnosed as having primary pulmonary hypertension are presented. The natural history, the physiologic manifestations, the pathology, and the proposed etiologies of the disease are discussed.

CASE REPORTS

Case Report #1

Mrs. L. W., a 48-year-old homemaker, was first admitted to Rush-Presbyterian-St. Luke's Medical Center on December 2, 1968, complaining of progressively increasing abdomoinal girth of two years' duration, two-to-three pillow orthopnea and peripheral edema of one year's duration, paroxysmal nocturnal dyspnea, marked dyspnea on exertion, occasional hemoptysis, and chest pain and syncope related to exertion, all of five months' duration. The pain was described as substernal and left precordial heaviness which was relieved by stopping all activity. The patient denied pleuritic-type chest pain. The hemotypsis varied from pink-tinged sputum to gross blood, and frequently occurred during nocturnal coughing episodes. Three syncopal episodes were associated with carrying groceries or fast walking, and two with doing housework. Mrs. L.W. denied any prodrome prior to the syncopal episodes, but noted that she was usually fatigued prior to their occurrence. She did not have urinary or fecal incontinence with these episodes.

She stated that at age 18 she had begun noticing some shortness of breath with exertion and had been told by a physician that she had an "enlarged heart," the etiology of which was not explored. Her two sisters had died of "heart disease" at ages 18 and 28 respectively. Her mother had died of "heart disease" at age 65. During the previous two years, local physicians had been treating the patient with a digitalis preparation and diuretics. These medications and the dosages prescribed had obviously varied, as had the patient's consistency in taking them. She had been admittd to another hospital in 1956, 1965 and 1968, and had been told each time that she had an "enlarged heart" and "heart failure." Her main complaint on the first two admissions was dyspnea on exertion. During the third admission she apparently had anasarca and was treated with intravenous diuretics, losing 12 pounds of body weight. Her weight had progressively increased after discharge. She admitted to having smoked one pack of cigarettes daily for the previous 20 years, but believing that this had contributed to her dyspnea, had stopped smoking six months prior to admission. She had no significant alcohol intake, and had taken no medication during the month prior to admission.

On physical examination, the blood pressure was 90/60 mm Hg, pulse 110 beats per minute and regular, respirations 36 per minute and moderately labored, rectal temperature 99 degrees F., and weight 132 pounds. The patient appeared chronically ill and in moderate respiratory distress. yet was alert and oriented. Anasarca, central and peripheral cyanosis, and three-plus clubbing of the digits were noted. Funduscopic examination revealed neither retinopathy nor papilledema. The palate was of normal contour. External jugular veins were distended to the mandible with the patient sitting upright, and prominent *a* and *v* waves were noted. Examination of the heart revealed a diffuse apical impulse in the anterior axillary line and a four-plus left parasternal lift. No thrills were present. The first heart sound was moderately diminished and the pulmonic closure sound was markedly accentuated and palpable. A loud systolic ejection click was palpable in the second and third left intercostal spaces. A third heart sound (or summation gallop) was audible at the lower left sternal border, as was a Grade III/VI harsh pansystolic murmur, the intensity of which appeared to increase with inspiration. This murmur radiated to the cardiac apex. A Grade I-II/VI decrescendo diastolic blowing murmur was localized to the area of the systolic ejection click, and a Grade I-II/VI diastolic rumble was present at the lower

left sternal border. Examination of the lungs revealed fine, moist rales to the mid-lung fields, bilaterally. No wheezes or pleural rubs were audible. Examination of the abdomen revealed moderately tense ascites. The liver was ballotable and could be percussed to a 16 cm span. It was firm, pulsatile, and slightly tender to pressure. The spleen tip was palpable 2 cm below the left costal margin. There was four-plus pitting edema of the lower extremities as well as three-plus presacral edema. Neurological examination was normal.

Admission arterial blood gases, with the patient breathing room air, revealed a pH of 7.40, pO_2 of 57 mm Hg, pCO_2 of 43 mm Hg, saturation of 72 percent, and base excess of plus 4.4 mEq/1. Electrocardiogram was interpreted as sinus tachycardia with a normal P-R interval and normal QRS duration, right axis deviation, right atrial enlargement, and right ventricular hypertrophy of a systolic overload pattern (Fig. 1). Admission urinalysis was

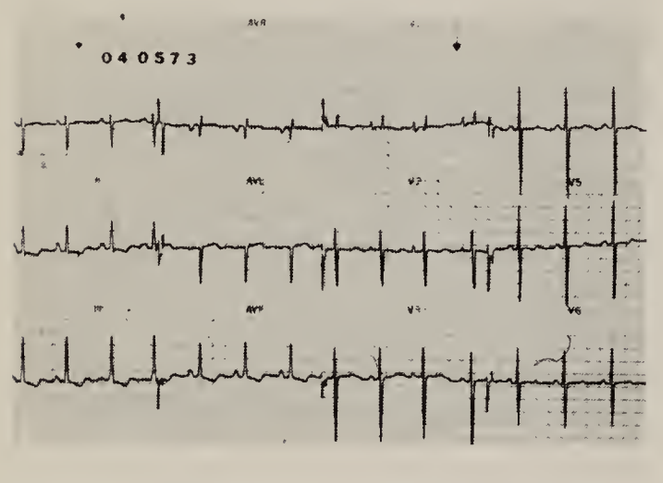
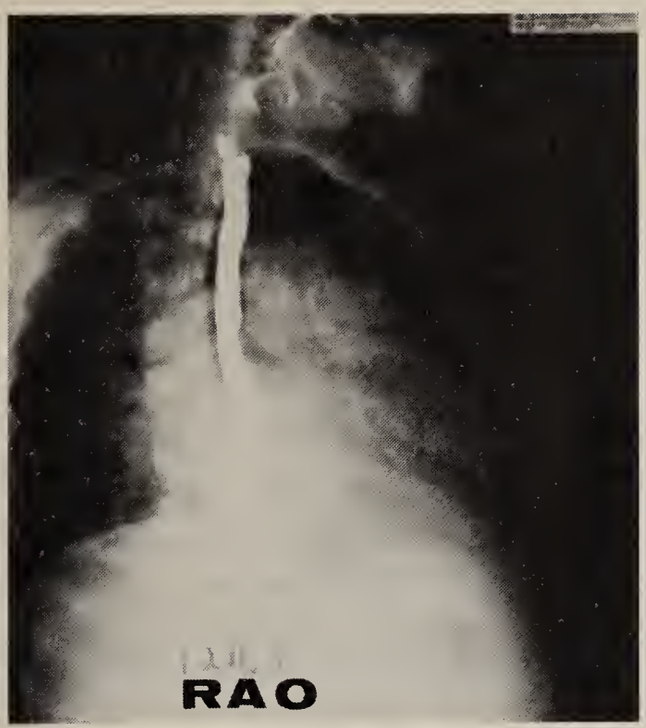


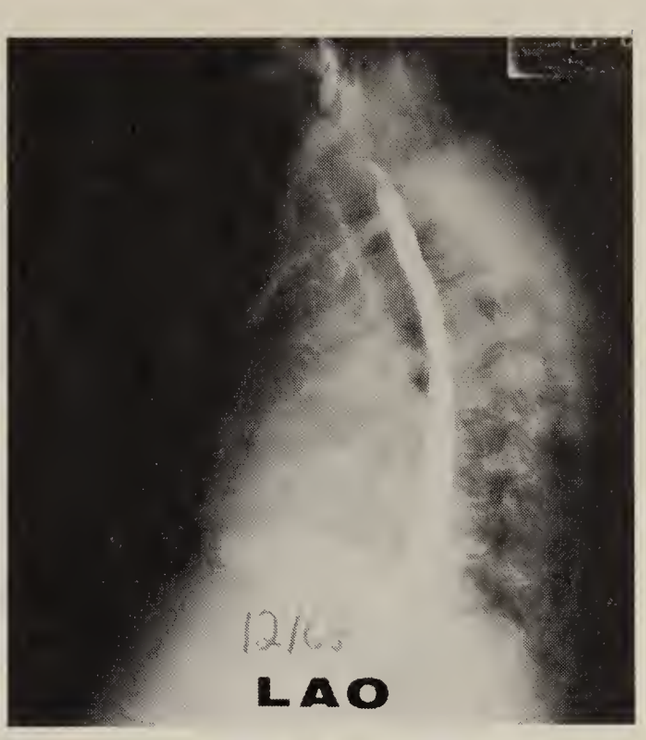
Fig. 1—Representative electrocardiogram from a subsequent admission of patient L. W.

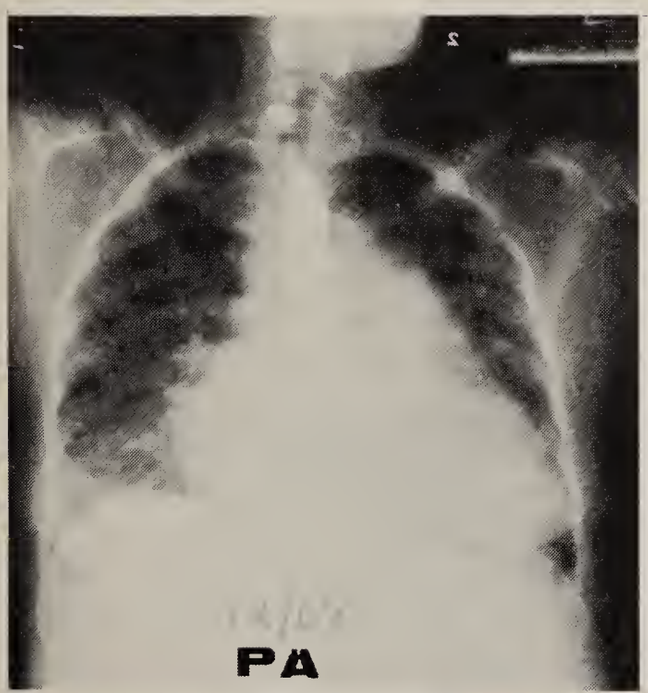
normal, and complete blood count showed a hemoglobin of 12.2 grams, hematocrit of 37 percent, and white blood cell count of 5,000 with a normal white cell differential. Admission electrolytes were normal except for a carbon dioxide content of 32.5 mEq/1. Blood urea nitrogen was 39 mg percent, and serum creatine 1.7 mg percent. Serum creatine phosphokinase was 8 units (normal, less than 18 units), serum glutamic-oxalacetic transaminase 410 units/ml (normal, 10-35 units/ml), serum glutamic-pyruvic transaminase 295 units/ml (normal, 5-30 units/ml), serum lactic dehydrogenase 920 units/ml (normal, 200-400 units/ml), and serum alkaline phosphatase 2.9 Bessey-Lowry units (normal, 0.6-2.5 B-L units). Total serum bilirubin was 1.2 mg percent with a direct fraction of 0.5 mg percent. Serum protein studies revealed a slightly depressed albumin fraction, and prothrombin time was 44 percent of control. Serum uric acid content was 9.0 mg percent.

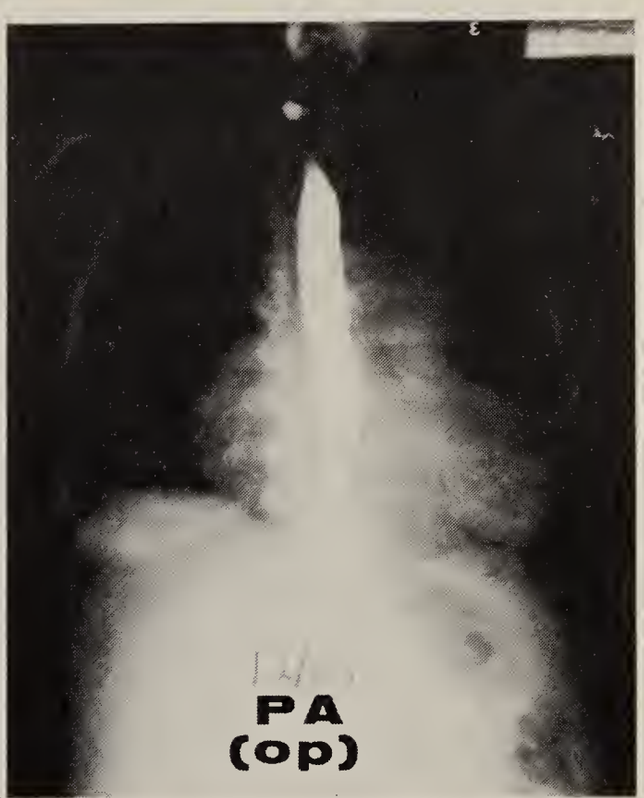
The patient was kept at bed rest, given humidified oxygen continuously and treated with intravenous diuretics and digitalis. Vigorous diuresis was obtained, and over the first six days of hospitalization the patient lost 22 pounds in body weight. By the sixth day there was complete resolution of the peripheral edema and a decrease in liver span and amount of ascites; the neck veins remained distended to the mandible. The patient's body weight appeared to plateau at 110 pounds, and dual isotope studies using ^{51}Cr and RISA revealed a red blood cell mass of 36.2 ml/kg body weight, a plasma volume of 68.7 mg/kg body weight, and a blood volume of 104.9 ml/kg body weight, with all values corrected for ideal height and body weight and moderately elevated. Barium swallow cardiac series (Fig. 2) was interpreted as showing marked prominence of the main pulmonary artery and central vasculature, severe right ventricular enlargement, an enlarged right atrium, little if any left ventricular enlargement, probable displacement of the left ventricle by the large right ventricle, and no left atrial enlargement. Bilateral cervical ribs were noted.

On the eighth hospital day the patient underwent cardiac catheterization. Catheterization data can be seen in Table I. Diagnoses entertained prior to study were atrial septal defect with Eisenmenger syndrome, primary pulmonary hypertension, and recurrent pulmonary emboli. The cardiac index was moderately depressed with the patient at a basal state. Severe pulmonary hypertension was present, with the









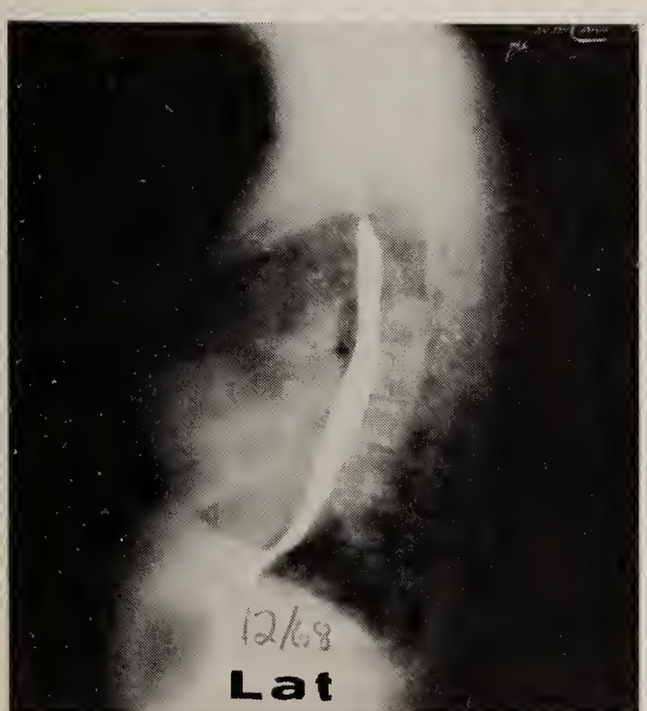


Fig. 2—Barium swallow cardiac series of patient L. W. (RAO=right anterior oblique; PA=posteroanterior; OP=overpenerated; LAO=left anterior oblique; LAT=lateral).

TABLE I

CARDIAC CATHETERIZATION DATA OF PATIENT L.W.

Pressures (mm Hg)	Systolic	End-Diastolic	Mean
Right atrium			24
Right ventricle	92	23	
Pulmonary artery	106	71	81
Pulmonary capillary wedge			11
Aorta	95	64	77
Left ventricle	95	10	
		Systemic	**Pulmonary**
Blood flow (liters/minute)		2.88	2.88
Blood flow index (liters/minute/m^2)		1.92	1.92
	Total Systemic	**Total Pulmonary**	**Pulmonary Arteriolar**
Resistances (dyne•sec•cm^{-5})	2135	2246	1941

pulmonary artery systolic pressure higher than the systemic systolic pressure, and the pulmonary arteriolar resistance 90 percent of the total systemic resistance. The normal pulmonary capillary wedge pressure excluded pathology at the mitral valve or pulmonary venous level. Ascorbate detection studies could document neither left-to-right nor right-to-left shunting of blood but did document tricuspid and pulmonic insufficiency. Blood samples from various cardiac chambers including an incidentally noted large coronary sinus, and from the great vessels, were also incompatible with blood flow shunts. By catheter passage, a presistent left superior vena cava and both a markedly enlarged right atrium and right ventricle were noted. With the patient breathing 30 percent oxygen, an arterial pO_2 of 74 mm Hg was obtained; when she was breathing 100 percent oxygen, an arterial pO_2 of 262 mm Hg was obtained. These data eliminated the possibility of any but minimal intrapulmonary shunting. Because of hazard to the patient, no contrast material was injected.

The study, therefore, supported the diagnosis of idiopathic or primary pulmonary hypertension. Subsequent studies revealed no evidence for collagen vascular disease. The patient was discharged on digoxin 0.25 mg daily, furosemide 120 mg twice daily, and spironolactone 25 mg four times daily. She was instructed in following a low salt diet and arrangements were made for oxygen therapy at home.

The patient remained stable at home, performed her daily activities and required only intermittent adjustment of diuretic therapy. In April, 1971, a vulvar lesion was noted, and subsequent biopsy revealed a highly invasive squamous cell carcinoma. Since Mrs. L. W. had remained quite stable as an outpatient, with no deterioration in her cardiopulmonary or renal status, and since her life expectancy was not certain, all physicians concerned with her care elected to perform the necessary curative surgery, realizing the great surgical risks. Under general anesthesia a radical vulvectomy with bilateral groin dissection was performed on May 11, 1971. Many of the expected complications occurred; but after ten weeks the patient was able to return home, a functional individual, maintaining the medical regimen previously described. She became lost to follow-up in the early part of 1973. On April 2, 1973, she presented in a condition similar to her first hospital admission here. She was hospitalized and diuresed. Her electrocardiogram continued to show the previously described features, the rhythm remaining a sinus node mechanism. The patient's fourth and last admission to

Presbyterian-St. Luke's Hospital was on June 1, 1973; she presented in a semi-comatose state with acute renal failure. Immediately prior to this admission, her electrocardiogram had begun to show multiple supraventricular arrhythmias, including multifocal atrial tachycardia, a wandering atrial pacemaker at rates less than 100 beats per minute, and atrial fibrillation. Premature ventricular beats conducted in a left bundle branch block pattern, and thus thought to originate in the right ventricle, were also present. During the hospitalization the patient did not respond to initial vigorous therapeutic efforts, and her demise occurred on June 5, 1973.

At post-mortem examination, the heart weighed 500 gm, with a markedly enlarged atrium containing an organized mural thrombus (Fig. 3), a markedly enlarged and hypertrophied right ventricle, a small left atrium with a diameter of 3 cm, and a left ventricle of normal caliber. The coronary arteries showed modest atherosclerosis with no occlusive lesions. The markedly thickened right ventricle was not well-endowed with a coronary arterial system. The foramen ovale was closed and the ventricular septum intact. The coronary sinus, measuring 6 cm in circumference, received two veins, thought to represent hemiazygos veins, at its apex in the area of the obtuse margin of the left heart. A persistent left superior vena cava was present. The tricuspid valve measured 23 cm in circumference with only slight thickening of the valve leaflets. The pulmonic valve was bicuspid (Fig. 4) with the valve ring measuring 8 cm in circumference. The pulmonary trunk was markedly dilated, and the pulmonary arterial tree was markedly ectatic and involved with moderate atherosclerosis; its branches could be dissected to within a few millimeters of the pleural surface (Fig. 5). No vascular emboli were present. The entire pulmonary venous drainage was received by the left atrium, and dissection of these

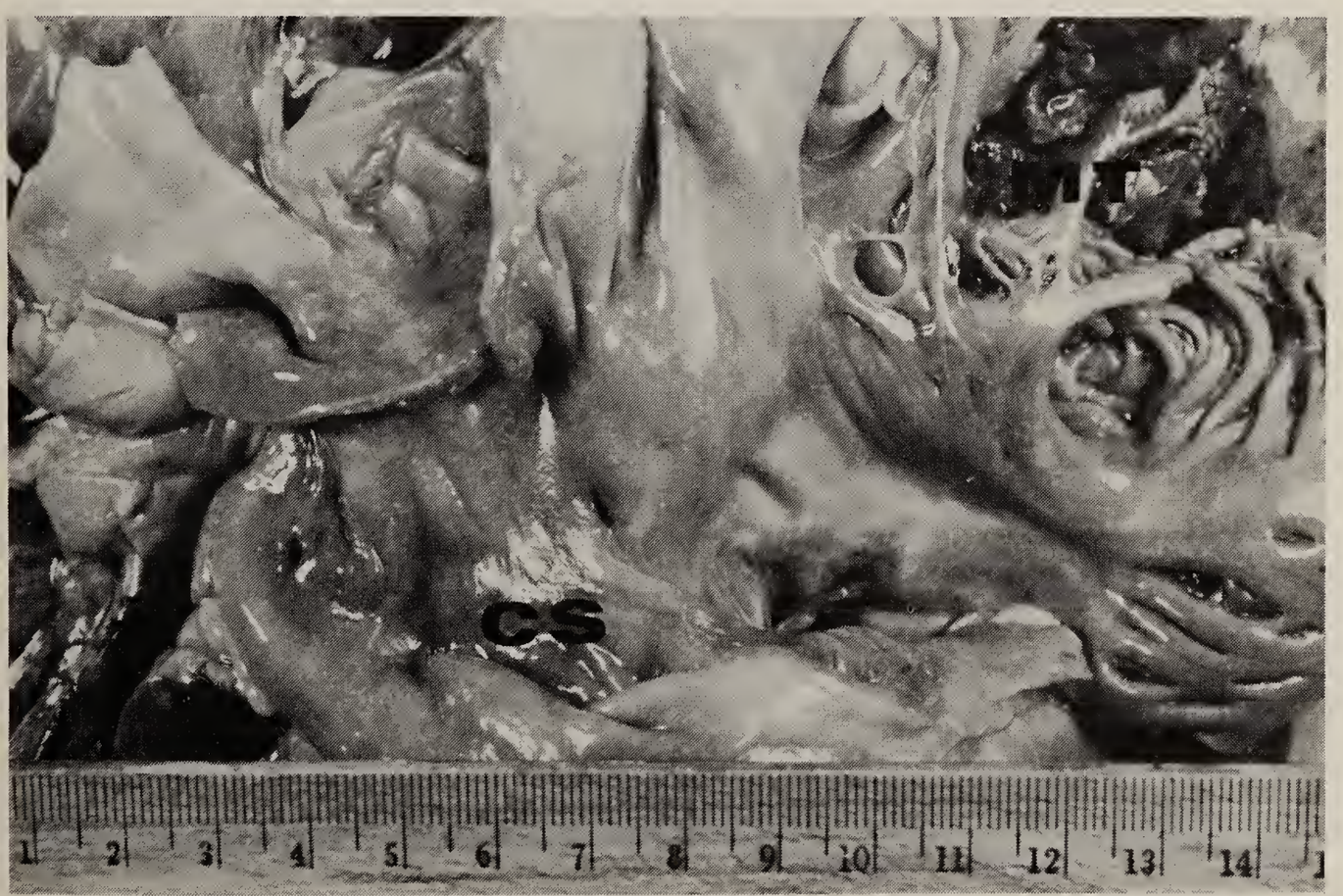


Fig. 3—Necropsy specimen of patient L. W., showing dilated right atrium with large coronary sinus (CS) and mural thrombus (MT—upper right corner).

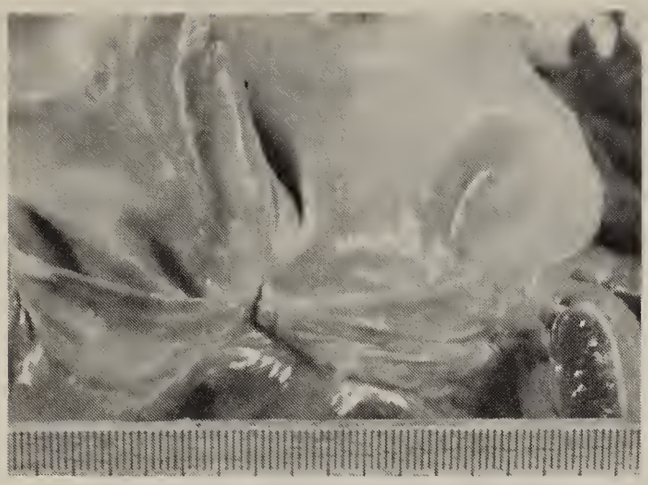


Fig. 4—Necropsy specimen of patient L.W., showing bicuspid pulmonic valve and dilated pulmonary trunk.

veins failed to reveal any pulmonary venous obstruction. The veins were not thickened, and the mitral valve was normal, the orifice admitting two fingers. The aortic valve and left ventricular outflow tract were also normal.

The lungs showed moderate anthracosis without emphysematous changes. No vascular anomalies were present and the tracheobronchial tree was not inflamed. The pleura was not thickened, and exhibited only a few areas of old adhesions. Histology of the lungs revealed extensive interstitial fibrosis with intra-alveolar edema and occasional clusters of hemosiderinladen macrophages. The interstitium was collagenous and hyalinized, with a paucity of fibroblasts and blood vessels. The intima of the arterial system was markedly thickened, and the media moderately so. The veins appeared normal. Special stains revealed small arteries and arterioles with thickened walls and lumina occluded by intimal proliferation. Plexiform lesions and microscopic unorganized and organizing thrombi plugging the lumina of small arteries were also present (Fig. 6).

The pathologist concluded that the patient did not have pulmonary hypertension

Fig. 5—Necropsy specimen of patient L. W., showing ectatic pulmonary arterial branches with atheromatous involvement.

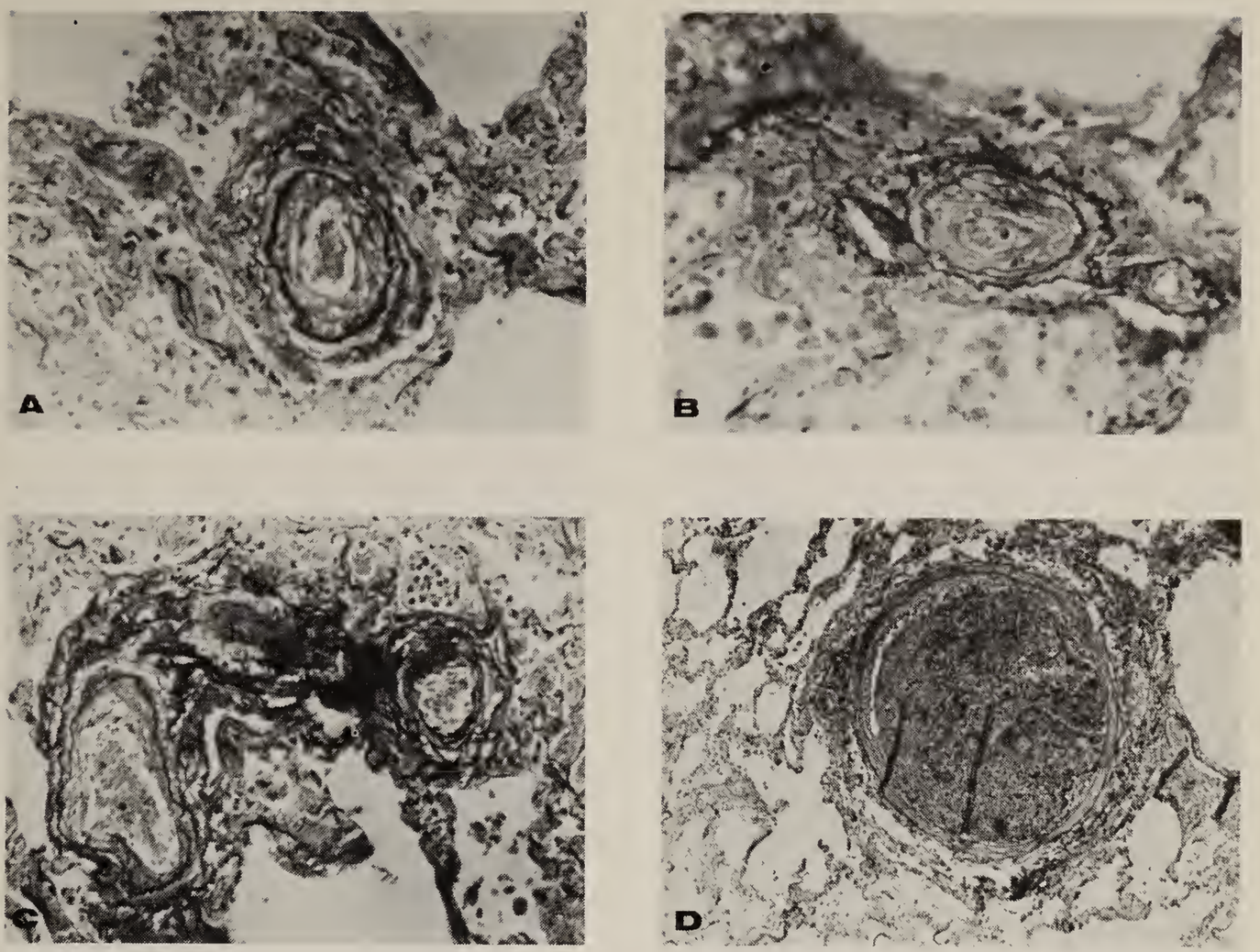


Fig. 6—Lung history of patient L. W. at autopsy. Elastic tissue-van Giesen stain. (A) and (B) Varying degrees of intimal proliferation with luminal obstruction, original magnification x 150. (C) Plexiform lesion, original magnification × 150. (D) Thrombus occluding small artery, and showing signs of early organization, original magnification × 125.

as a result of congenital or acquired cardiac disease or an anomalous pulmonary vascular tree. The presence of interstitial pulmonary fibrosis could have either caused or resulted from the severe pulmonary arterial damage. In the absence of any active inflamatory process in the interstitium at autopsy, or evidence of a pneumoconiosis suggesting that the interstitial fibrosis was secondary, all available information indicated the best diagnosis to be idiopathic or primary pulmonary hypertension.

Case Report #2

Mrs. S. W., a 21-year-old architect, was admitted to RPSLMC on March 18, 1974, for elective cardiac catherization. At age 12 she had begun to experience, on exertion, lightheadedness and syncope preceded by dyspnea. There was no aura preceding these episodes and they were not associated with urinary or fecal incontinence. At that time a recommendation for cardiac catheterization was refused by her parents. The patient limited her activity by not participating in any sports requiring physical exertion. When lightheaded episodes did occur, she found she could abort a syncopal episode by sitting down and placing her head between her knees. She also noted palpitations during and following these episodes, describing her rate and rhythm as fast and regular. During the 10 months prior to admission. she had begun to notice dyspnea and lightheadedness when climbing two flights of stairs, and occasionally a dull aching chest pain, usually occurring with physical

activity and relieved within two to five minutes by rest. In September, 1973, her voioce had suddenly become hoarse. An otolaryngologist disqovered paralysis of her left vocal cord and told her that it was related to her heart disease. Two weeks prior to admission she had a syncopal episode while running up stairs. She denied leg pain, hemoptysis, pleuritic pain, or symptoms of chronic pulmonary or systemic congestion. She also denied Raynaud's phenomenon, as well as myalgias and arthralgias. She had no history of systemic hypertension. diabetes mellitus, or rheumatic fever, and had always been of normal or less than normal body weight for her height. There was no family history of systemic hypertension, diabetes mellitus, coronary artery disease, congenital heart disease or collagen disease. Her review of systems was negative except for a retinal detachment in her left eye. She also had had an intrauterine device placed for contraception after her recent marriage. She had never used tobacco and rarely drank alcohol.

Physical examination revealed a blood pressure of 100/68 mm Hg in both arms, pulse 84 beats per minute and regular, and oral temperature of 98 degrees F. The patient was noted to have a slight malar flush. There were no obvious skeletal anomalies and the palate was of normal contour. The nailbeds were slightly dusky with signs of early clubbing. The neck veins were not distended and the carotid upstrokes were normal. Heart examination revealed a poorly localized apical impulse 10 cm from the midsternal line. A one-to-two-plus left parasternal lift was present with no thrills. The first heart sound was normal, and the pulmonic component of the second heart sound was markedly accentuated, with physiologic splitting present. A loud early systolic ejection click, heard on auscultation in the second and third left intercostal spaces, was also palpable in those areas. There was no third or fourth heart sound. A Grade II/VI scratchy systolic murmur was heard maximally at the upper left sternal border and disappeared with Valsalva maneuver. No diastolic murmurs were present. The remainder of the physical examination was normal except for a small retinal scar in the left fundus.

Admission electrocardiogram (Fig. 7) showed normal sinus rhythm with a normal PR interval and QRS duration, right axis deviation, and right ventricular hypertrophy of a systolic overload pattern. Bar-

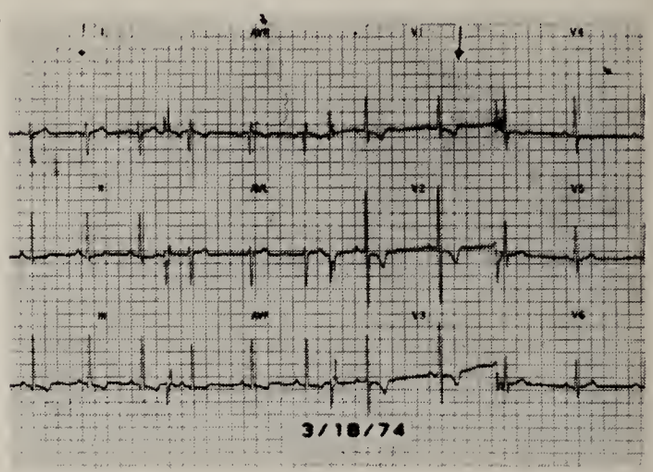
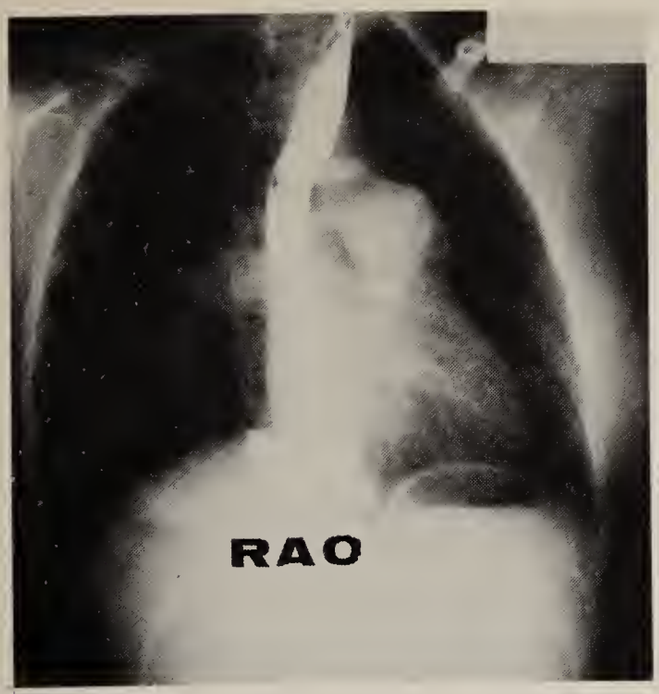
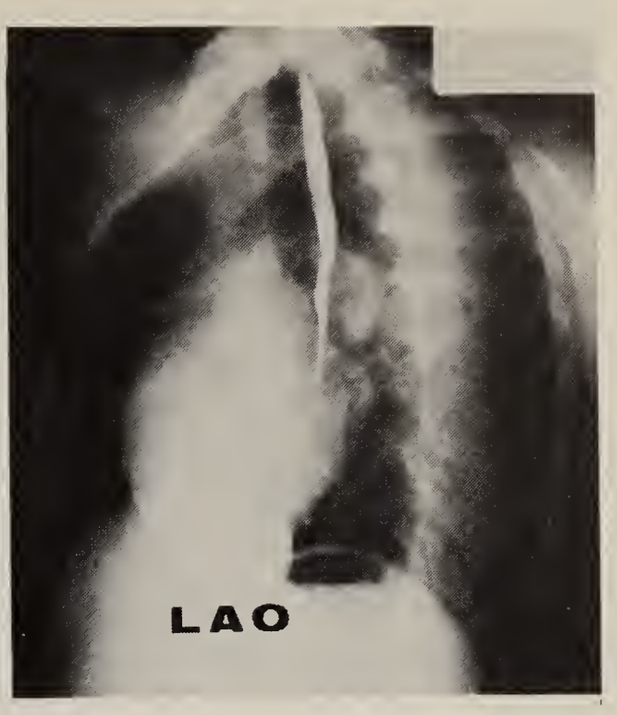


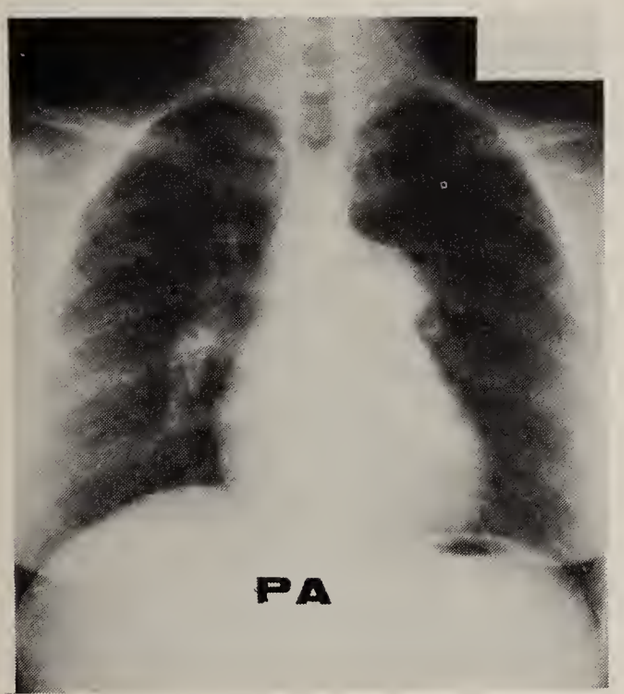
Fig. 7—Electrocardiogram of patient S. W.

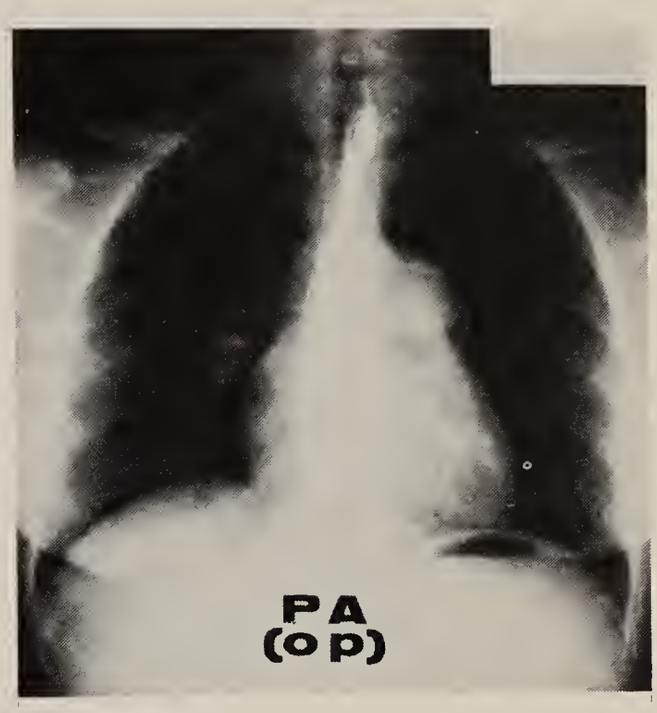
ium swallow cardiac series (Fig. 8) showed right ventricular enlargement without evidence of other chamber enlargement. The pulmonary trunk was moderately dilated, as were the left and right pulmonary arteries. There was some suggestion of attenuation of the peripheral vasculature. The lung parenchymal fields were normal. Subsequent phonocardiography documented the auscultatory findings. An SMA-18 profile, a coagulation profile, a thyroid battery, and a collagen disease profile were all normal.

In light of all the available information, the most likely diagnosis was primary pulmonary hypertension. More remote diagnoses considered were valvular pulmonic stenosis and atrial septal defect with an Eisenmenger syndrome. Evidence against valvular pulmonic stenosis was the loud pulmonic component of the second heart sound, the dilated primary two branches of the main pulmonary artery, and the low intensity systolic murmur. Evidence









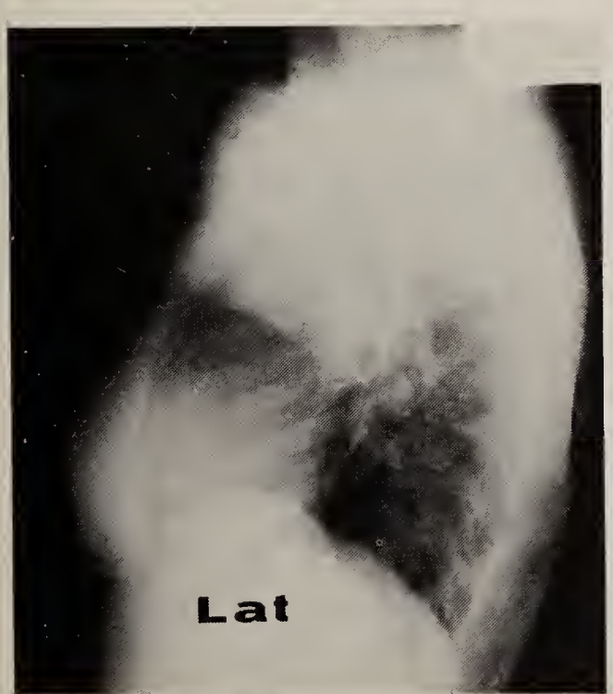


Fig. 8—Barium swallow cardiac series of patient S. W. (RAO=right anterior oblique; PA=posteroanterior; OP=overpenetrated; LAO=left anterior oblique; LAT=lateral).

against an atrial septal defect with an Eisenmenger syndrome was the duration of the history and the normal physiologic splitting of the second heart sound.

Cardiac catheterization data are summarized in Table II. The cardiac index was moderately depressed at rest with the patient at slightly less than the basal state, and an inappropriate rise was seen with adequate exercise. Ascorbate detection studies and blood sampling documented neither a left-to-right nor a right-to-left blood flow shunt. Severe pulmonary hypertension was present with the pulmonary artery systolic pressure 81 percent and 126 percent of the aortic systolic pressure at rest and exercise respectively. At exercise the pulmonary arteriolar resistance was essentially equal to the total systemic resistance. The pulmonary capillary wedge pressure remained normal during rest and exercise, excluding mitral valvular and pulmonary venous pathology. No valvular or intraventricular gradients were present. The patient's arterial blood gases were normal at rest. With the patient breathing 40 percent oxygen for 10 minutes, an arterial pO_2 of 282 mm Hg was obtained, again eliminating anything but trivial intrapulmonary shunting. No contrast material was injected because of hazard to the patient, and the study was totally in support of primary pulmonary hypertension. Subsequent pulmonary function tests were normal except for a borderline low diffusion capacity.

At discharge the patient was advised that any strenuous physical activity should be avoided, but that slow bicycle riding, light housework and sexual intercourse were acceptable. She was also to consider a Teflon injection of her left vocal cord to mitigate her hoarseness.

NATURAL HISTORY

Little is known about the natural history of primary pulmonary hypertension. The likelihood of both a congenital and an acquired type exists, and this will be discussed under *Possible Etiologies.* In a series of 23 patients reported by Walcott et al,[1] 19 were female and four were male, a ratio of 5:1. The median age was 34, with a range from 11 to 56 years at the time of death. Only two patients were under the age of 15. More than half of the patients were dead within three years after onset of symptoms and three patients survived longer than a decade. Median

TABLE II

CARDIAC CATHETERIZATION DATA OF PATIENT S.W.

	Rest			Exercise		
Pressures (mm Hg)	**Systolic**	**End-Diastolic**	**Mean**	**Systolic**	**End-Diastolic**	**Mean**
Right atrium			2			2
Right ventricle	73	3		125	2	
Pulmonary artery	79	38	53	132	62	89
Pulmonary capillary wedge			3			6
Aorta	98	66	81	105	70	86
Left ventricle	96		8			

	Systemic	**Pulmonary**	**Systemic**	**Pulmonary**
Blood Flow (liters/minute)	3.27	3.27	6.50	6.50
Blood Flow Index (liters/minute/m^2)	2.08	2.08	4.14	4.14

	Total Systemic	**Total Pulmonary**	**Total Arteriolar**	**Total Systemic**	**Total Pulmonary**	**Total Arteriolar**
Resistances (dyne•sec•cm^{-5})	1931	1295	1222	1033	1095	1021

survival time after onset of symptoms was 2.5 years. The study also showed that 96 percent of the patients presented with dyspnea and 26 percent with syncope and chest pain.

All of the presenting symptoms in primary pulmonary hypertension appear to result from a low cardiac output. Dyspnea on exertion has been related both to a decreased cardiac output and to increased pulmonary artery pressure at rest and during exercise. Syncope similarly seems to result from associated diminished cerebral blood flow.[2] Anginal chest pain is usually precipitated by exertion and may last from a few seconds to half an hour; nitroglycerin has been found to be minimally effective in relief, but inhalation of oxygen has been found to be beneficial. The concept of right ventricular angina is attractive but the chief evidence against it is the inefficacy of nitroglycerin in relieving anginal symptoms. The paucity of coronary blood supply to the markedly enlarged right ventricle, as found at post-mortem examination in one of our patients, conceivably could account for nitroglycerin failure. It has been proposed that the pain arises in the pulmonary artery itself and is the direct result of distention of the vessel.[3] Stuckey[4] found that such chest pain occurred in conditions in which the cardiac output was low and relatively fixed.

One of our patients had left vocal cord paralysis. In 1897, Ortner[5] reported that recurrent laryngeal nerve paralysis occurred in approximately 0.5 percent of patients with mitral stenosis (Ortner's syndrome). and concluded that the nerve was compressed by the enlarged left atrium. Pathological study, however, has shown that dilatation of the pulmonary artery is most contributory, with the nerve compressed between the dilated left pulmonary artery and the aorta or arterial ligament.[6] Other investigators have reported that lymph nodes in the triangle formed by the pulmonary artery, aortic arch, and arterial ligament may effectively compress the left recurrent laryngeal nerve when accompanied by cardiac hypertrophy, pulmonary artery dilatation, or both.[7]

A variety of supraventricular and ventricular arrhythmias appears only to occur late in the course of the disease, and, invariably, the patient is in sinus rhythm, frequently sinus tachycardia, when the disease first becomes symptomatic.[1]

CLINICAL MANIFESTATIONS

Clinical assessment of primary pulmonary hypertension requires an understanding of acoustic signs that directly reflect elevations in pulmonary hypertension of any etiology. Primary pulmonary hypertension serves as "ground-zero" for a group of diseases, and reflects the most unmodified manifestations of elevated pressure in the lesser circulation. In this context, the auscultatory events, and phonocardiographic events if performed, can be directly related to the effects of pulmonary arterial hypertension *per se.*

The loud pulmonic closure sound emphasized by Steell[8] comes closest to being unique to pulmonary hypertension. ". . . accentuation of the pulmonary second sound is always present, the closure of the semilunar valves being generally perceptible to the hand placed over the pulmonary area, as a sharp 'thud'." If the second sound cannot be separated into its two elements, one can compare the summated sound in the second right and in the second left interspace and can consider that an increase in the latter area may be due to accentuation of the pulmonic component. Splitting of the second sound at the apex is a sign suggesting elevated pulmonary arterial pressure, since an accentuated pulmonic closure sound may be transmitted as far as the cardiac apex.[9]

The pulmonic ejection sound can often be palpated as a sharp impact overlying the systolic pulsation of the dilated, hypertensive pulmonary artery. The sound is identified acoustically by its high-pitched, sharp, clicking quality, its location in the second and third left intercostal spaces, and often, its selective attenuation during inspiration and amplification during expiration. Respiratory variation in intensity is not a feature of aortic ejection sounds. The duration of right ventricular isomet-

ric contraction determines the interval between the tricuspid component of the first heart sound and the pulmonic ejection sound. It generally follows that the higher the pulmonary arterial diastolic pressure, the later the onset of right ventricular ejection, and the later the onset of the ejection sound.[10]

Pulmonary hypertension, by stressing the right ventricle, may cause functional incompetence of the tricuspid valve. The murmur of tricuspid regurgitation is best detected at the lower left sternal border, although it may radiate from this area to the cardiac apex, especially when the apex is formed by the right ventricle. The quality can be high-pitched, musical or harsh, and inspiratory augmentation of the murmur, Carvallo's sign, is a feature of recognized diagnostic importance.[11] Inspiratory amplification of the murmur reflects the functional ability of the right ventricle to convert the inspiratory increment in venous return into an increase in stroke volume and regurgitant flow. Consequently, with advanced degrees of right ventricular failure this ability may be lacking, with the resulting loss of Carvallo's sign. In this context, absence of inspiratory amplification does not exclude the presence of tricuspid insufficiency.

A mid-diastolic rumble may also be audible at the lower left sternal border. The murmur may be confined to presystole and may appear with or become amplified by inspiration. These murmurs have been ascribed to relative tricuspid stenosis from dilatation of the right ventricle.[12] Mid-diastolic murmurs may occur in pure tricuspid regurgitation and may relate to the increased rate of atrioventricular flow, a mechanism that can become operative in pulmonary hypertension should the tricuspid valve become incompetent.[13] The interesting concept of the right-sided Austin Flint murmur has been proposed to explain diastolic rumbles occurring with pulmonary hypertensive regurgitation.[14]

The Graham Steell murmur of pulmonic insufficiency is usually confined to the second and third left intercostal spaces adjacent to the sternum.[8] The increased diastolic pressure in the pulmonary artery causes a high velocity of regurgitant flow and hence the high-frequency, blowing quality of the murmur. Since the elevated pressure exerted upon the incompetent valve begins at the moment the right ventricular and pulmonary pressure pulses cross (dicrotic notch), the murmur begins with or immediately after the accentuated sound of pulmonic valve closure. The intensity of the murmur may be sufficient to generate a thrill or may be soft and variable to the point of equivocation.

In pulmonary hypertension the stressed right ventricle may need the help of strong atrial contraction so that large *a* waves may be seen in the jugular venous pulse, presystolic distention of the right ventricle may be palpated, and atrial sounds may accompany this presystolic distention. The sounds are most readily detected at the lower left sternal border, although they may be transmitted to the apex or toward the left base.[9] The inspiratory increase in venous return may augment both right atrial contraction and right ventricular presystolic distention and may therefore cause the right-sided atrial sound to become amplified or appear earlier. Exercise or leg raising may have similar effects.

A right-sided third heart sound occurs during the rapid filling phase of the cardiac cycle and is a sign of ventricular failure or augmented atrioventricular flow rate.[9] The sound is of low frequency and best heard at the lower left sternal border but, again, may be audible at the apex if the right ventricle occupies the apex. The sound may become amplified should tricuspid regurgitation accelerate flow during rapid ventricular filling.

Roentgenographic changes resulting from pulmonary hypertension are variable, and, discouragingly, there is no established contour-pattern of right ventricular enlargement. On the PA view, enlargement of the right ventricle—with or without concomitant enlargement of the right atrium—more frequently than not produces a nondescript or overall enlargement of the cardiac silhouette, displacing the right atrial border to the right and the left heart bor-

der to the left, frequently with an "uplifting" effect on the apex. In the lateral and oblique views the enlarged right ventricle forms a convex border below the pulmonary artery and can be seen encroaching upon or obliterating the substernal space. Where the right ventricle enlarges greatly, it may rotate the left ventricle posteriorly and thereby simulate left ventricular enlargement. Furthermore, muscular hypertrophy of the right ventricular wall may not be associated with definite enlargement, even in the presence of considerable pulmonary hypertension. This seems to be more often the case in instances of chronic bronchitis-emphysema where the heart shadow is normal or mildly enlarged on the plain film despite a definitely hypertrophied right ventricle.[15]

The so-called "classic" vascular features of primary pulmonary hypertension seen on radiographs are marked enlargement of the main pulmonary artery and its primary branches with striking decrease in size of the medium-sized vessels.[16] In one of our patients, however, the peripheral pulmonary vascular markings appeared normal rather than decreased. The same was true in 80 per cent of patients in the study previously cited,[1] and some patients had enlargement of medium sized vessels simulating that of shunt vessels. On the PA view, one sees a "filling in" of the space below the aortic knob by the dilated pulmonary trunk. Using the lateral and oblique views, one can ascertain dilatation of the left and right pulmonary arteries.

The electrocardiogram in pulmonary hypertension frequently shows right axis deviation (mean QRS vector greater than plus 110 degrees), right atrial enlargement (P waves in lead II 0.25 mV or greater and prominent positive P vector in lead V_1), and right ventricular hypertrophy of the systolic overload pattern (pure R or QR complex in lead V_1). These findings would appear to be almost universal at the onset of symptoms in the patient with primary pulmonary hypertension,[1] but the differential diagnosis that these electrocardiographic changes present must always be kept in mind.[17]

PATHOLOGY

Cardiac catheterization is a necessary procedure in many patients with pulmonary hypertension, particularly when valvular or shunt lesions may be present, and surgical correction can ameliorate the disease. The Eisenmenger syndrome usually develops in early childhood in the patient who has shunting of blood at the cardiac or great vessel level, and one rarely encounters this complication in the adult patient; the two most common congenital cardiac shunt lesions in the adult population are atrial and ventricular septal defects.[18] One study, however, indicates that patients with atrial septal defects may develop the Eisenmenger syndrome later in life; they may represent a special group.[19] Long-term follow-up studies also indicate the presence of a disproportionate number of patients with Eisenmenger syndrome in the third decade and beyond, perhaps indicative of a significant amount of late progression.[20,21] The pulmonary hypertension which accompanies congenital left-to-right shunts is potentially reversible when the shunt is such that pulmonary blood flow is appreciably increased. As a rule, there is a high mortality rate attendant upon surgical correction of the shunt lesion when there is little or no left-to-right shunt, or when there is some right-to-left shunt accompanying pulmonary pressure and resistance at the systemic level.[22,23]

Wagenvoort and Wagenvoort[24] performed morphologic and morphometric studies on pulmonary vessels in lung tissue from 156 patients for whom a diagnosis of primary pulmonary hypertension had been made, either by cardiac catheterization or on the basis of clinical findings. Of this number, 46 patients were found to have other etiologies of their pulmonary hypertension including chronic thromboembolism, chronic pulmonary venous hypertension, pulmonary veno-occlusive disease, sarcoidosis, chronic bronchitis-emphysema, and pulmonary schistosomiasis. There was no failure to make the diagnosis in those patients who had cardiac catheteri-

zation, and the foregoing data, plus all the other available information concerning the patient, were considered. The aforementioned report, as well as that of Walcott,[1] mentions the controversy concerning the hazards of cardiac catheterization in the patient with primary pulmonary hypertension. In a cooperative study, only one complication was reported during 92 procedures carried out in patients in whom the diagnosis was confirmed.[25] It is known from experience that angiocardiography is an extremely risky procedure in patients with advanced disease, a fixed capacity pulmonary vascular bed, and a systemic blood pressure which may only be maintained by vasoconstriction. In such cases the sudden fall in systemic arteriolar resistance caused by the contrast material may result in catastrophic hypotension and cardiac arrest.[26] DeBono[27] found that the pulmonary artery pressure increased significantly following injection of contrast material. He hypothesized that the reason for the increased pressure was the upsetting of electrostatic charges on the surface of the red cells, with resultant red cell clumping and sludging in the small vessels, and that this might lead to almost total cessation of circulation through the lungs. The obvious consequence would be impairment in flow to the left side of the heart and to the coronary arteries, resulting in marked cardiac ischemia, hypoxia, and arrhythmias. Another possibility may be that the chemical effects of the contrast material cause marked reflex vasoconstriction, contributing to the already-reduced pulmonary blood flow.

Pathophysiologically, it would appear that the lung has a limited number of reactions to prolonged severe pulmonary hypertension, and it is often unclear which comes first, the vascular lesions or the pulmonary hypertension. In primary pulmonary hypertensive patients studied at autopsy,[1] virtually all have a dilated pulmonary arterial trunk with atherosclerotic plaques extending into dilated primary and secondary branches. The atherosclerosis varies from mild to severe, and the atherosclerotic plaques infrequently contain cholesterol clefts. Medial muscular hypertrophy is present in a mild to moderate degree, and degenerative medial changes are characterized by hyalinization and thinning of the muscular wall with narrowing and separation of fibers. Intimal proliferation would appear to be the most striking finding, and this has been found to be different from that of other pulmonary hypertensive patients by nature of its concentric, laminar structure, usually with an "onion-skin" type of arrangement.[24]

Plexiform lesions probably have the most direct effect on lumen diameter of larger vessels.[28] In such cases, blood must pass through a network of capillary-sized channels embedded in proliferated endothelial cells and fibrous tissue before it can reach the distal alveolar capillary bed. In some cases, such structures are interposed proximal to most of the alveolar capillary bed. The resistance to blood flow through such structures is presumed to be very great. The dilated vascular channels may represent a compensatory response which serves to increase pulmonary blood flow. Walcott[1] found that at cardiac catheterization, reduction in the pulmonary blood flow index to levels below 1.5 l/min/M^2 was accompanied by more advanced grades of pulmonary plexiform lesions and by arteriolar occlusive changes at autopsy. Wagenvoort[29] has mounted several arguments against a congenital nature of plexiform lesions; these lesions are known to appear in cardiac shunt malformations which are accompanied by pulmonary hypertension.

POSSIBLE ETIOLOGIES

Gore and Tanaka[30] adequately demonstrated that primary pulmonary hypertension is a diagnosis of exclusion and recurrent pulmonary thromboembolism is the condition most difficult to exclude. Walcott[1] has presented an extensive argument against recurrent pulmonary emboli as the etiology of primary pulmonary hypertension, and certainly pulmonary thromboembolism complicates right heart failure of many kinds, particularly when mural

thrombi are present in the right atrium or ventricle. Some instances of recurrent unrecognizable pulmonary thromboembolism will be indistinguishable clinically and pathologically from primary pulmonary hypertension. If primary pulmonary hypertension is the result of repeated microemboli or fragmented large emboli, it is a distinct variant of the usual thromboembolic process in which the small thrombus is resorbed. Kingdon et al[31] first postulated that retention of thrombi is related to a disorder in blood coagulation or clot lysis in small pulmonary vessels, and Inglesby et al[32] recently reported seven members of a kindred who had antiplasmin levels which were abnormally elevated; five members of the kindred had pulmonary hypertension. The impaired fibrinolytic activity was found in vitro and the authors suggest that in vivo inhibition of fibrinolysis of recurrent pulmonary microemboli may be responsible for the pulmonary hypertension in the five members. Familial occurrence of pulmonary hypertension has been reported by others and may be transmitted in an autosomal dominant mode.[33,34] The fact that one of our patients had two female siblings who died at an early age of unknown heart disease made it likely that her disease was congenital.

Other etiologic possibilities which have been considered in primary pulmonary hypertension have been congenital defect in the pulmonary vasculature, variant of collagen disease, and vasospasm of the pulmonary arteries. Edwards[35] used the phrase "carry-over of the fetal type of vessel" to indicate that under certain circumstances the pulmonary arteries remain thick-walled after birth, implying that the thick media should be considered a congenital malformation causing pulmonary hypertension; others feel it is more probably a response to abnormal hemodynamic or functional stimuli prevailing at the time.[24]

One-third of the patients reported by Walcott[1] had Raynaud's phenomenon, and some had arthritis, as well as serum gamma globulin abnormalities. Rawson and Waske[36] were the first to suggest that primary pulmonary hypertension was related to the collagen diseases. In their study, Raynaud's phenomenon appeared to precede the symptoms of pulmonary hypertension by many years, but members of several of the patients' families suffered from Raynaud's disease without developing pulmonary hypertension.

Wood[37] suggested that vasoconstrictive factors may play a role in primary pulmonary hypertension. In many cases of the disease, the pulmonary arterial pressure and resistance could be lowered by such drugs as acetylcholine, tolazine and other vasodilators,[38] though without lasting effects. Samet and Bernstein[39] showed a sharp decrease in pulmonary arterial pressure in a patient with primary pulmonary hypertension after the intracardiac infusion of acetylcholine; but three years later, when the procedure was repeated in the same patient, there was no effect. Wagenvoort[24] suggests that the medial hypertrophy is a result of increased vascular tone and changes in arterial pH, and daily activities such as sleep have been shown to have a pronounced effect on pulmonary artery pressures. Hypoxia is known to produce constriction of the muscular pulmonary arteries but the exact mechanism by which this happens is unknown. Pulmonary hypertension of high altitude appears to be the prototype of an essential pulmonary vasospastic process. In some asymptomatic subjects pulmonary hypertension becomes severe following exercise at altitude and reverts to normal at sea level.[40]

Finally, the prevalence of primary pulmonary hypertension in adult women in contrast to the equal sex ratio in children may lead one to suspect that factors related to sexual maturity in the female are involved; this remains to be investigated.

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APPENDIX

Pulmonary vascular resistance (and systemic vascular resistance) is commonly expressed as dyne•sec•cm^{-5}. The general resistance formula is:

$$\text{Resistance} = \frac{\text{pressure difference}}{\text{flow}}$$

From standard clinical measurements of pressure and cardiac output:

$$\text{Resistance} = \frac{\text{mm Hg}}{\text{cm}^3/\text{min}}.$$

Converting mm Hg to centimeter•gram•second units:

1 cm Hg × 980 cm/sec^2 × 13.6 gm/cm^3 =
13320 dynes/cm^2 or 1332 dynes/cm^2 per mm Hg

Where a dyne is the force equivalent to a 1 gm mass put through an acceleration of 1 cm/sec^2, 980 cm/sec ^{2} is the acceleration of gravity, and 13.6 gm/cm^3 is the specific gravity of Hg.

Therefore:

$$\frac{\text{Pressure gradient in mm Hg} \times 1332 \text{ dynes/cm}^2 \times 60 \text{ sec/min}}{\text{Flow in cm}^3/\text{min}}$$

$$= \text{Resistance in dyne•sec•cm}^{-5}$$

Or:

$$\frac{\text{Pressure gradient in mm Hg} \times 79920}{\text{Flow in cm}^3/\text{min}}$$

$$= \text{Resistance in dyne•sec•cm}^{-5}$$

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THE DEVELOPMENT OF SURGERY IN RUSSIA

Anatoly Bezkorovainy

(EDITOR'S NOTE: This is the third in Dr. Bezkorovainy's series of articles on the history of medicine and allied sciences in Russia.)

ABSTRACT. Surgery was introduced into Russia abruptly by royal edict in the 18th century. The field was at first dominated by military surgeons, the most famous of whom were Nicholas Arendt, Leonid Nagumovich, and Peter Dubovitskii. With the development of the universities in Russia, the field of surgery was introduced into civilian population, and the academic surgeons thus assumed a dominating position. The most prominent of these was Nicholas Pirogov, often called the father of Russian surgery. He is credited with being one of the first to use ether in anesthetic surgery in 1847 and with devising the osteoplastic foot amputation technique. Other prominent surgeons of Pirogov's era were Adelmann, Szymanovsky, Vladimirov and Sabaneev. Abdominal surgery was introduced by the gynecologists, Krassovsky being the first to perform an ovariectomy in Russia.

Antisepsis and asepsis were introduced by Pelekhin, Sklifossovskii, Federov, and Slaviansky. Of the more modern pre-World War I surgeons, in Russia, the names of Bobrov, co-discoverer of the Bobrov-Champagnier hernia operation, and discoverer of the corrective operation for spina bifida, and that of Veliaminov are most prominent. The most famous Russian expatriate surgeon was Ernest v. Bergmann, who departed in 1878 to occupy the chair of surgery in Berlin.

INTRODUCTION

The origins of western European surgery are hidden somewhere between the trephiners of ancient Egypt and the school of barber-surgeons of the baroque period. In Russia, on the other hand, there were no barber-surgeons, and surgery was, along with the other medical specialties, introduced into that country by royal invitation. The influx of foreign-trained physicians was greatest during the 18th century, especially during the reign of Catherine the Great (1762-1796) when such men as Joseph von Mohrenheim of Vienna and Christoph E. H. Knachstedt of Braunschweig were called to teach surgery in Russian medical schools.

THE EARLY PERIOD OF RUSSIAN SURGERY

The 18th and 19th century Russian surgery was dominated by military surgeons, and most of Russia's more prominent civilian surgeons could trace their background to the army or navy. Russian military surgery apparently reached its highest degree of efficiency during the Russo-Japanese war (1904-1905), and was an object of study by many foreign medical officers. Of special interest was the Russian method of performing abdominal surgery on the wounded as soon as possible after the wound was inflicted. For this purpose there were a number of hospital railroad

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trains functioning in the nearest possible proximity to the battle line, and equipped with all the standard surgical and medical facilities. Of special prominence in connection with Russian hospital trains was a female surgeon, Princess Vera Ignatievna Gedroits, who performed complicated surgery practically within the range of Japanese rifles.[1]

Among pioneering Russian military and court surgeons there are many who were associated with events of historical importance, if not with far-reaching medical discoveries. One such better-known surgeon was Karl v. Espenberg (1761-1822), who was born in the Estonian province of Russia.* He joined the Russian navy, and made the round-the-world cruise with Adm. Krusenstern (1802-1806). A peninsula near the Cape of Good Hope is named after him (Cape Espenberg). A physician who took part in many events of historical importance was Leonid Nagumovich (1792-1853). Nagumovich, an army surgeon, was with the troops in battles against Napoleon at Borodino, Maloyaroslavets, Lützen, Kulm, and Leipzig. Later, he participated in the storming of Warsaw that ended the Polish rebellion of 1831. Nagumovich published numerous works in the field of military medicine.

Among early Court physicians, the best known is Pajanota Condoidi, a Greek by birth, brought to Russia in his childhood. He studied medicine at Leyden, receiving his doctorate in 1733. In Russia he was head of the Medical Chancellery in addition to his duties as Court physician. He died in 1760. Another Court physician of some accomplishment was Ivan Enokhin (1791-1863), who accompanied Nicholas I on many military expeditions.

Of the more academically-oriented Russian surgeons in that early period one can mention Peter Dubovitskii (1815-1867) and Nicholas Arendt (1780-1859). The former was a graduate of Moscow University, and was one of the first surgery professors of Kazan University (1837). In 1841, Dubovitskii went to the Military-Medical Academy in St. Petersburg, where he served as the Academy's president from 1851 to 1867. He published his own medical journal between 1843 and 1848. Nicholas Arendt[2] is said to have been the most prominent Russian surgeon before Pirogov (see below). He was primarily a military doctor, but was also a personal physician to Tsar Nicholas I. He participated in the Prussian campaign (1806-07), the Swedish campaign (1808-09), and the Napoleonic war (1812-1814). He was especially well known for his method of tying blood vessels.

Before the advent of antiseptic techniques in the latter half of the 19th century, surgical procedures in general were largely limited to amputations of the extremities, the removal of topical tumors or other lesions, and the removal of stones from the genito-urinary system. The problem of bladder stones was especially acute in central Rusia, so that in the 1860's as many as 20 percent of all surgical beds in that area's hospitals were occupied by patients with stones.[3] Most stones examined were of mixed character: a uric acid nucleus, followed by a layer of calcium oxalate, and finally a layer of phosphates. There was also a large frequency of pure phosphate stones. Uric acid stones were rare in Russia in contrast to Germany, France, and England. Oxalate stones were most common in children and young adults, whereas phosphate and urate stones were seen mostly in older people. Klien[3] felt that the high frequency of stones observed in the populace of central Russia was caused by a local diet largely of vegetables and the frequent intake of acidic beverages, such as the fermented bread beverage, kvas.

Removal of stones was done by the lithotomy method, since lithotripsy apparently gave a larger mortality rate. The Moscow University surgical clinic reported a mortality rate of 12 percent among 4486 lithotomies performed, compared to a rate of 14 percent in England and France. Elias Buyalsky (1789-1864) is said to have been one of the most skillful Russian stone surgeons of the time.

*Now the Estonian Soviet Socialist Republic.

THE FATHER OF RUSSIAN SURGERY: NICHOLAS I. PIROGOV

One of the first Russian surgeons to attain world prominence, and the man who made surgery a truly respectable medical specialty in Russia was Nicholas I. Pirogov. He has been honored for his accomplishments by both the pre- and post-revolutionary governments, as well as by Russia's medical profession, which instituted a tradition of annual medical meetings in his memory (Pirogov Medical Congresses).

Pirogov was born in Moscow in 1810. He entered the Moscow University at 14 and graduated from its Medical School in 1827. After post-graduate work at Dorpat, (Russia), Pirogov went abroad to study with the Weber brothers in Leipzig, Rokitansky in Vienna, and Schönlein in Zurich. He returned to Russia in 1835, and a year later was appointed to a faculty position in the surgery department of Dorpat University, thus becoming one of the first Russians to be admitted to the faculty of that Baltic German-dominated establishment.

In 1840, Pirogov moved to St. Petersburg to occupy the chair of surgery at the Military-Medical Academy. Upon his insistence, a surgical clinic was established under the chair of surgery. This was an important event for, in spite of the great potential of the surgical approach to the treatment of disease, which was evident by the middle of the 19th century, the civilian medical establishment of Russia was reluctant to grant surgery a place equal to that of therapeutic medicine in hospitals and medical schools. According to Walther[4] this was due to the fact that in all civilian medical establishments, the directing physicians were internists, who apparently did not like surgeons and insisted upon the rotation of all staff physicians through all of the hospital's departments. This was supposedly done to prevent overspecialization among doctors, though the effect was, in many cases, a failure to develop skillful surgeons in many of Russia's hospitals. For this reason, it was imperative that the Military-Medical Academy, the most prestigious medical school in Russia, point the way by establishing a surgical clinic. In spite of this, the Kiev University Medical Faculty resisted establishing a surgical clinic as late as 1861!

Pirogov's pedagogic activities were frequently interrupted by his participation in various military campaigns of that era, such as the Caucasian campaign of 1847, where he first used ether as an anesthetic, and the Crimean war of 1855-56. During the latter, Pirogov organized a nurses' corps to help with the wounded, and fought, up to the Emperor himself, for the improvement of conditions in military hospitals. In 1856 he resigned his position at St. Petersburg, and was appointed to oversee the development of the educational system in southern Russia. In 1861 Pirogov was appointed to study educational centers abroad for the purpose of recommending institutions where Russian students could receive the best possible postgraduate education. Thereafter, he spent some four years abroad, and upon returning to Russia, retired to his estate to occupy his time with writing and practicing medicine. He died in 1881.

Pirogov made many contributions to medicine.[5] As indicated above, he was one of the first physicians in Europe to use ether as an anesthetic, in 1847, though, contrary to the method of his western colleagues, he preferred to administer it rectally. In 1852 he also instituted the use of frozen body sections as an aid in the study of anatomy. Pirogov wrote extensively on the subject of military medicine drawing from his experiences gathered during the wars in the Caucasus and Crimea.[6] His works differed from those of his British and French counterparts in that, instead of merely presenting casualty statistics, Pirogov wrote mostly of methods he believed would diminish mortality and morbidity rates among the wounded. He felt that proper organization of the medical aid system, proper nursing care of the wounded, and minimization of transporting the wounded were far more important than the quantity and skill of attending surgeons.

Pirogov, being a military surgeon at heart, is perhaps best known in the West for his technique for the osteoplastic amputation of the foot. It is known today as the Pirogov-Syne operation.[5]

OTHER FAMOUS RUSSIAN AMPUTATORS AND ORTHOPEDIC SURGEONS

The tradition of excellence created by Pirogov at Dorpat was very ably continued by Georg Adelmann (1811-1888), who assumed Dorpat's chair of surgery upon the departure of Pirogov.[7] Adelmann was born and educated in Germany, going to Dorpat in 1841 upon the recommendation of Chelius. Here he remained for 30 years, the customary length of service in the Russian civil service, and then retired to Berlin. In Dorpat, Adelmann trained an entire generation of Russian surgeons, among them Szymanovsky, Grube, Bornhaupt, and Reyher. Adelmann's contributions to surgery were many, including a method for performing splenectomy, and the still-used Adelmann's maneuver for amputation of the finger.

At Dorpat, one of the ablest students of Adelmann was one Julius Szymanovsky,[4] born in 1829 in Riga (Livonian province of Russia*) and said to have been of Polish origin related to the Polish royal family and the dukes of Kurland. By the time of his birth, however, Szymanovsky's family had become completely germanized, so that Szymanovsky could not even speak correct Russian to the day he died. This language difficulty created special problems during his activities as a professor at Kiev University, though it did not appear to have particularly disturbed the students. At any rate, in spite of his language problem, Szymanovsky was able to write an excellent text on plastic surgery ("Dermatoplastic") in the Russian language in 1865. Most of his research papers, however, were published in German. As noted previously Szymanovsky received his medical education at Dorpat under Adelmann, graduating in 1856. By 1858 he was professor of surgery at Helsingfors University (now in Finland), and in 1861 he moved to Kiev University in the same capacity. Szymanovsky's brilliant career was cut short by a malignant tumor, and, in spite of surgery by no other than Pirogov himself, he succumbed to his disease in 1868 at the age of 38.

Szymanovsky's work included new contributions to the fields of surgical instrumentation and procedures, *e.g.*., a concave chisel to resect portions of the hip joint, the design of a cast that immobilized the entire pelvic area, a technique for pelvic surgery,[8] modification of Pirogov's osteoplastic foot amputation technique,[9] and the advocacy of foot surgery on the basis of its anatomy and function as a locomotor device.[10] He also developed a technique for the post-operative care of amputation wounds, in which the stump was permitted to heal while immersed in cold water.[11] This method minimized both the morbidity and mortality rates in the surgical wards of Dorpat university hospitals, where an overall mortality rate of "only" 22.9 percent was reported following amputations. This rate was very good by the pre-antiseptic standards of the early 1860's. Szymanovsky explained the beneficial effects of immersion therapy on the basis that air was excluded from the wound, and that pus forming in the wound would sink to the bottom of the immersion fluid.

Szymanovsky was an ardent advocate of the conservative approach to surgery. In this connection he reported on two cases of cerebral hernia that were at first mistaken for cysts.[12] The first case involved a 19-year old girl. Szymanovsky began operating for the removal of the "cyst," but upon incision of the skin, he found an artery that was not supposed to be present in that location. Proceeeding more cautiously, he punctured the tumor and obtained a clear fluid similar to cerebrospinal fluid. Realizing that he had exposed the dura mater, he immediately closed the wound. Contrary to the experience of other surgeons, his patient survived without developing meningitis, and was dis-

*Now in Latvian Soviet Socialist Republic.

charged from the hospital with the instruction to wear a protective covering over the lesion.

In another instance, a soldier came to the hospital with a similar tumor on the side of the head. Other physicians had diagnosed a cyst and were ready to operate but Szymanovsky believed he recognized the lesion as another case of cerebral hernia. He did not permit surgery and recommended that the soldier be discharged from the military service. However, the patient declined, and was discharged from the hospital with the same instruction as Szymanovsky's first patient.

In both cases lesions were present on the side (temporal bone vicinity) of the head—one on the left, the other on the right side—of completely healthy individuals. The tumors apparently had been there for as long as the patients could remember, and Szymanovsky concluded they were of congenital defect origin. He urged surgeons to carefully investigate the history of all cysts to be removed, and if such tumors were found to be present from birth, to forego surgery, lest the patient develop meningitis and die.

After the appearance of the above work,[12] a certain Dr. Mamorsky from Kiev published a paper questioning Szymanovsky's approach to cyst removal. The soldier discharged by Szymanovsky apparently had attempted to have his tumor removed elsewhere and had consulted Mamorsky. The latter obliged and operated on the soldier, finding that the tumor was not a cerebral hernia after all, but a congenital cyst. It was removed, and the soldier was finally happy. Mamorsky therefore advised, in cases of doubt, probing at the base of the tumor until reaching the bone, as would happen if the tumor were a simple cyst, or until eliciting cerebral symptoms as would be the case if the lesion were a cerebral hernia.

Szymanovsky's wrath at this attitude knew no bounds.[13] He noted that Mamorsky's paper was written because his gamble had paid off and the patient survived. Had Szymanovsky been right and had the patient indeed been suffering from a cerebral hernia, Mamorsky would have done an autopsy instead of writing a paper. In cases like this, Szymanovsky advised, it was better for the patient's sake not to take the risk of surgery and to learn to live with the tumor.

Szymanovsky's sentiments were strongly supported by Georg Jaesche, the developer of the Jaesche-Arlt operation.[14] He reminded the medical profession (this was still in the pre-antisepsis era) that even simple operations carried a high risk of mortality, and cited in evidence his own experience with 13 relatively uncomplicated procedures (*e.g.*, correction of foot defects) in which six patients had expired.[15] Jaesche also reported on a case similar to Szymanovsky's, where a patient was making excellent progress after brain surgery. However, as soon as the patient got up for the first time following surgery, he collapsed and died immediately.[16] Jaesche wrote that persons like Marmorsky, who unnecessarily take risks with patient's lives may be successful occasionally, but sooner or later Providence would slap them into a greater degree of humility through the suffering and needless deaths of their patients.

Several Russian surgeons other than Pirogov and Szymanovsky made significant innovations in osteoplastic and orthopedic surgery. One of these, Vladimir Vladimirov (1837-1903), was the developer of the tarsectomy procedure.[17] Vladimirov was a graduate of Kazan University (1860) and after working in Germany and France for about two years, returned to Kazan as a university assistant. There he defended his doctoral thesis, the subject of which was a new osteoplastic operation on the foot whereby the astragalus and calcaneus only were removed, leaving the rest of the foot intact. This procedure, known as tarsectomy was rediscovered five years afterwards, in 1877, by the German Johann Mikulicz. Consequently it is also known as the Vladimirov-Mikulicz operation. Vladimirov tried twice for appointment to the chair of surgery at Kazan University. Unsuccessful in this, he devoted most of his professional life to Zemstvo service (local

community medical practice) and private practice. Towards the end of his life, Vladimirov fell upon hard times, the result of the miserly Zemstvo pension, and made his home in a hotel room. He died of gangrene in the Penza Zemstvo hospital and was buried in the hospital's cemetery. The author of Vladimirov's obituary[17] bitterly contrasted the life of the Russian surgeon with that of his counterpart, Johann Mikulicz. The latter had a coveted university appointment in Breslau, a large private surgical clinic, and spacious villa on expansive grounds. Vladimirov, though no less talented, had had to die in a small provincial hospital, neglected by nearly everyone.

A surgeon who devoted most of his efforts to osteoplastic and orthopedic surgery was Ivan F. Sabaneev (b. 1858), a graduate of Kiev University and professor at Odessa University. He emigrated to Turkey following the Bolshevik coup, and his later fate is apparently unknown. Among several procedures proposed by Sabaneev, his osteoplastic resection of the knee joint is probably of greatest interest.[18] The operation was carried out mostly on patients with tuberculosis of the joints and involved the removal of patella and the bone endings of the femur and tibia, followed by joining the bone stumps. The muscular insertions were thus retained, and the wound was covered by the normal inner surface of the skin. Sabaneev is best known in the West for his development of the gastrostomy technique, which was also described by Rudolf Frank of Vienna. It is today known as the Sabaneev-Frank operation, and involves the construction of a fistula into the upper portion of the stomach for the purpose of artificial feeding. Sabaneev used this method on four patients, in whom the esophagus had been removed because of cancer.[19] The patients survived four days to two months, and autopsies of the longer survivors showed that the stomach-skin juncture had healed satisfactorily.

Other Russian orthopedic surgeons of some accomplishment included Robert R. Wreden (b. 1867), who is not to be confused with Robert Wreden, the otologist; and Sergei Saltykov (b. 1874). Saltykov was a graduate of Kharkov University, and worked abroad until the First World War. He then returned to Russia, only to leave after the Bolshevik coup. He finally settled in Zagreb, Yugoslavia as a professor of pathology. Saltykov's work involved mostly bone transplantation, and in one of his references[20] he mentions a Dr. Radzimovsky of Kiev University, who, in 1881, was apparently one of the first to recognize immunologically-mediated rejection of bone transplants. Up to that time it was believed that a bone transplant either "took" or "did not take," the reasons for negative results not being specified.

THE ADVENT OF ABDOMINAL SURGERY IN RUSSIA

Surgery, as stated above, was in the 1850's and 1860's mostly concerned with the amputation of damaged or gangrenous extremities, the removal of stones, and the excision of topical tumors. Abdominal surgery was not practiced because of the resultant high mortality rates from peritonitis and pyemia.

However, the development of huge ovarian cysts in some women prompted both the patient and the surgeon to undertake the risk in removal of such tumors that sometimes weighed 50 to 100 pounds. Abdominal surgery thus began both in western Europe and in Russia with ovariectomies. The first successful ovariectomy was performed in the United States in the early 1800's, but attempts in Europe met with little success and were not performed until the 1850's and 1860's. Thus by 1866, there had been performed 904 ovariectomies in the world, with a mortality rate of 41 percent. At that time, Russia accounted for 28 ovariectomies with a 43 percent mortality rate.[21] The first surgeon to perform a successful ovariectomy in Russia was Krassovsky (1821-1898),[22] in 1862. He was a graduate of the Military-Medical Academy (1851). Upon further study in Germany and France, he joined the St.

Petersburg Lying-In Hospital, and became its director in 1870. Among his contributions are the systematization of obstetric and gynecologic instruction in Russian medical schools and the training of numerous physicians in abdominal surgery.

Other surgeons who followed Krassovsky's example, included Szymanovsky, Grube, and Sklifossovsky.[23] The latter removed a 31-pound cyst from one woman, and a 54-pound tumor from another. Both patients survived the ordeal. The first bilateral ovariectomy in Russia was performed by Maslovsky, an assistant in Krassovsky's clinic.[21] He removed a 34-pound cyst from the left ovary of his patient, and a smaller one from her right ovary. The patient recovered uneventfully. It may be noted that all of these operations were performed without the benefit of antisepsis or aspesis, and this therefore must be considered a truly heroic period in the history of surgery.

ANTISEPTIC AND ASEPTIC TECHNIQUES IN RUSSIA

Antiseptic technique was introduced into Russia by Paul P. Pelekhin (1842-1917), who published the first papers on the subject in Russia in 1868 and 1869 shortly after visiting Lister's clinic in England. He was sent to the United States to study methods of military surgery, especially the experiences in handling casualties during the American Civil War. Pelekhin was on the faculty of the Military-Medical Academy, retiring from service in 1889. His efforts in the field of antisepsis were expanded by Nicholas Sklifossovsky (1836-1904), who in the 1880's designed the surgical clinics for antiseptic surgery at Moscow University. Aseptic techniques were popularized by Sergei P. Fedorov, who in 1893 installed Russia's first autoclave, at Moscow University. An ingenious method for the purification of air in the operating room was devised in 1890 by Dr. Sapeshko, a gynecologist in Prof. Rein's gynecological clinic at Kiev University. Sapeshko had installed a water pipe system that sprayed a fine aerosol of water throughout the operating room before surgery was started. This process precipitated all dust and air-borne bacteria.[24]

The man who introduced aseptic techniques into the delivery rooms of Russia was Leonid v. Slaviansky (1847-1898), a student of Krassovsky and graduate of the Military-Medical Academy.[25] He reported that as a result of these measures, the mortality rates from puerperal sepsis had dropped to 0.3 to 0.5 percent by 1890 in Russia's obstetric clinics.

The discussion of the field of aseptic surgery cannot be complete without mentioning Ernest von Bergmann (1836-1907). He was born in the Livonian province* in the city of Riga and educated at Dorpat, under Adelmann. He was in the Prussian service from 1866 to 1870 and took part in the Franco-Prussian war. In 1871 he joined the faculty at Dorpat, leaving Russia in 1878 to assume the chair of surgery in Berlin vacated by Langenbeck. Bergmann's contributions to surgery were varied and numerous. He is credited with developing steam sterilization (1886), the discovery of the anti-bacterial properties of mercuric salts, and with bridging the gap between 19th century antiseptic surgery and the 20th century aseptic technique. Most of these far-reaching discoveries were made by Bergmann during his activity in Berlin, and their detailed discussion is thus beyond the scope of the present work.

ANESTHESIA

The methodology of anesthesia practiced in Russia paralleled that of western Europe. As stated above, Pirogov was one of the first physicians in Europe to use ether for this purpose; however, ether was later largely replaced by chloroform. An area of anesthesiology pioneered in Russia was the intravenous administration of anesthetics. The most popular compound used in this manner was hedonal (ethyl carbamate or urethane), first proposed for this purpose in 1895 by Schmiedeberg.

*Now in Latvian Soviet Socialist Republic.

Soviet postage stamps honoring surgeons Sklifossovsky (left) and Pirogov (right).

Hedonal was first tried on dogs, then on human subjects by Kravkov, a professor of pharmacology in St. Petersburg,[26] who preferred to use intravenous hedonal (3 g) in conjunction with small doses of chloroform (10 to 15 g/hour). Fedorov used hedonal without the chloroform,[27,28] and noted that there were minimal after-effects following surgery, that the anesthetic did not bring about significant changes in respiration and pulse rates, and that no renal damage could be observed. Fedorov also noted that an intravenous anesthetic such as hedonal was especially useful in neck and head surgery, where the surgeon would not be hampered by a face mask.

In addition to his work in aseptic surgery and anesthesia, Fedorov (1869-1936) is also credited with establishing Russian urological surgery. He founded a urological society in St. Petersburg in 1907 and was vice-president of the International Urological Congress of 1914. His work involved development of techniques for the removal of stones from the urinary tract, electrocoagulation, and nephrectomy.[29] He is said to have installed Russia's first x-ray apparatus only a year after its discovery in 1895.

SOME MODERN RUSSIAN SURGEONS

A very prominent Moscow University surgeon, whom the Soviets consider to have established the Russian surgical school, was Alexander A. Bobrov (1850-1904). Numerous Russian surgeons were trained in his clinics, and he developed a number of new surgical techniques, such as the hernia operation (Bobrov-Champagnier method), the removal of liver cysts, and the corrective technique for spina bifida,[30] which was first used by Bobrov on an eight-year-old child, who had no

bowel or bladder control. After replacing the spinal cord in the spinal column, Bobrov grafted a piece of the ilium to the spinal column to cover the opening. Eventually, acceptable bowel and bladder controls were developed in the patient, and the child was discharged as cured. Bobrov considered his method to be best suitable for spina bifida in the sacral and sacrolumbar regions. For spina bifida in the higher regions of the spinal column, Bobrov suggested using a piece of rib as a grafting device.

One of the most versatile Russian surgeons and prolific contributors to surgical literature was Nicholas M. Volkovich (1858-1928), who was a student and later professor at Kiev University. He was responsible for establishing the Kiev Surgical Society in 1908. Volkovich's work involved several seemingly unrelated areas of surgery, such as plastic surgery of the nose, the repair of both male and female urogenital tracts, the removal of hemorrhoids for which purpose he constructed a special set of instruments,[31] and orthopedic surgery.

In this last area he was especially concerned with the handling of tuberculous joints, where he advocated a radical resection approach based on Sabaneev's and Vladimirov's experiences.[32] As much as possible, the joint was not to be disturbed, was sawed off at the top and bottom, and was then removed as one piece. Bone endings were then brought together so that no empty space remained in the appendage. He handled 28 patients in this manner. Volkovich also described a new symptom in chronic appendicitis.[33] He found that the tone and elasticity of the abdominal muscles on the right side were markedly decreased in such cases. He confirmed this observation using a tonometer designed by Exner and Tandler.

The most influential Russian surgeon in the years just preceding the Bolshevik coup was Nicholas A. Veliaminov (1855-1920), who was often asked to treat the Tsar and his family. Veliaminov was a graduate of Moscow University, served as a military surgeon between 1878 and 1884, and was appointed to the faculty of the Military-Medical Academy in 1894, serving as its president between 1910 and 1912. During the Russo-Japanese and First World wars, Veliaminov directed in a major capacity the medical services of the Russian armed forces. He was the founder of the St. Petersburg Surgical Society, and of the first major Russian surgical journal, *Khirurgicheskii Vestnik* (1885). It merged with another Russian surgical publication, called *Letopis' Russkoi Khirurgii* in 1894, and in 1902 became known as *Russkii Khirurgicheskii Arkhiv* (Russian Archives of Surgery). In 1910 it changed its name to *Veliaminov's Surgical Archives,* maintaining publication until 1917. Throughout this 32-year period of the journal's existence, Veliaminov served as its senior editor.

Veliaminov's contributions to medicine were concerned with disorders of the joints and the significance of endocrinology in surgical practice. In 1910 he published an extensive treatise on diseases of the joints and their classification. He was especially interested in tuberculous joints and the surgical treatment of tuberculosis in general. He was responsible for establishing an institution for tuberculous children on the Baltic Sea town of Wenden (Ventspils) in the then Kurland province of Russia.*

In 1908 Veliaminov published a paper describing a form of polyarthritis which he saw in patients who recovered from infectious diseases such as typhoid and scarlet fevers.[34] The disease was characterized by stiffness of all joints, muscular atrophy, damage to the spinal cord, and mediastinal goiter diagnosed by x-rays. He believed the causative agent of the polyarthritis was a toxin produced by the thyroid gland. He treated his patients with a thyroid extract, and one group experienced full recovery. In the other group, where no dramatic effects were observed following this therapy, full cure was effected by thyroidectomy. This apparent inconsistency was explained by Veliamin-

*Now in Latvian Soviet Socialist Republic.

ov as follows:[35] The goitrous thyroid gland produced toxic substances, which either enhanced the action of the thyroid hormone, or negated its effects. The former instance resulted in the typical Basedow disease symptoms; in the latter case a myxedema-type disease was produced, which Veliaminov called disthyresis. Thus, in some patients with the disthyresis-type toxemia, the administration of thyroid extract brought relief; in others the thyroid gland had to be removed. He believed that only the diseased portion of the thyroid gland was able to produce the toxin, whereas the healthy portion continued producing the normal thyroid hormone.

Veliaminov was the recipient of many honors, both in his native land and abroad. For instance, he was an honorary member of the British Royal College of Surgeons. The Soviet regime considers Veliaminov to have been one of the most distinguished Russian surgeons, and he occupies an honored place in most texts on the history of medicine printed in the Soviet Union. Veliaminov died of starvation following the Bolshevik coup, when he was apparently denied shelter and the means for subsistence, probably because of his association with the Tsar's household.

CONCLUSION

Following a period of dormancy and relative inactivity during the 18th and early 19th centuries, surgery developed rapidly in Russia to the point where on the eve of the First World War, it could boast of many first-rate surgical clinics and many important discoveries in the field of surgery. The works of Russian surgeons were printed in the West in German and French literature, and also to a large degree in domestic surgical journals. Such articles, written in Russian, were regularly abstracted in the German periodical, *Centralblatt für Chirurgie,* and are available to western scholars. It would, therefore, appear that statements such as the following, "Little is known of the Russian surgeons who wrote only in Russian, for very few of their works have been considered worth translating,"[36] which appeared in a recent book on the history of surgery, are largely untrue and counter-productive in establishing the role of Russian surgery with relation to modern surgical techniques.

In fact, the role of Russian medical institutions and Russian physicians in influencing medical practice in western Europe is quite large. Such names as Adelmann, v. Bergmann, Pirogov, and Jaesche have already been mentioned. One can, in addition, mention the most distinguished Russian gynecologic surgeon Vladimir F. Snegirev (1847-1916) whose texts on obstetrics and gynecology were extensively used in western Europe; Robert Wreden, a St. Petersburg otologist and ear surgeon, whose technique of perforating the tympanic membrane inspired Voltolini to devise his now-famous procedure;[37] and S. Logechnikov (1838-1911), a Moscow University ophthalmologist, who devised a surgical procedure for the treatment of glaucoma, which was later allegedly pirated by Knies from Heidelberg.[38]

The field of surgery in Russia was, of course, not unique in producing men who contributed much to the world's pool of surgical techniques, and, in turn, in enticing western practitioners to go to teach and practice in Russia. Many other medical specialists, as well as basic scientists, left Russia for more lucrative positions in western Europe: Oswald Schmiedeberg (1838-1921) the famous pharmacologist, who left Dorpat in 1872 to take the chair of pharmacology at the newly established Strassburg University; Wilhelm Ostwald, the chemist and Nobel prize winner, who left the Riga Polytechnic Institute to become a chemistry professor at Leipzig in 1887; and, of course, Ilie Mechnikov, the discoverer of phagocytosis and another Nobel prize winner, who established himself in Paris. The pre-World War I era was characterized by wide open communication among medical and scientific colleagues of eastern and western Europe for the benefit of all concerned.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Allergy

Schur S, Hyde JS, Wypych JI: Eggwhite sensitivity and atopic eczema. *J Allergy Clin Immunol 53,3:88, 1974*

Thirty-four children with atopic eczema were studied for eggwhite sensitivity. Clinical manifestations, skin deactivity to eggwhite antigen IgE, by radioimmunoassay (RIA) and specific reaginic IgE antibodies to eggwhite by the radioallergosorbent test (RAST) were evaluated. Patients were divided into two groups on the basis of clinical sensitivity to eggwhite antigen.

Of 13 eczematous patients in Group I with known clinical egg sensitivity, two had RAST levels between 0 and 24 percent, six between 25 and 100 percent, and five had RAST levels greater than 100 percent. In this group, five had positive prick skin tests to eggwhite.

Of 21 eczematous patients in Group II with no demonstrated clinical egg sensitivity, 17 had RAST levels of 0 to 24 percent, three had RAST levels between 25 and 100 percent, and one had a RAST level greater than 100 percent. In this group, three had positive prick tests to eggwhite.

The eggwhite RAST showed a significant correlation with clinical egg sensitivity ($p=0.0005$) and with a prick skin test of the same antigen ($p=0.036$) but not with total serum IgE levels. However, no correlation was found between clinical egg sensitivity and eggwhite prick skin test.

Biochemistry

McDonald RI, Shepro D, Rosenthal M, Booyse FM: Properties of cultured endothelial cells. *Ser Haemat 4:31, 1973*

Endothelial cells were obtained by several procedures from human, bovine and dog aortae and were successfully cultured *in vitro*. Cultures, established by "thrombinizing" the vessel intima, were subcultured for 18 passages and were found to maintain their structural phenotype. The cells contained numerous granules, microfilaments, golgi complex, extensive rough and smooth endoplasmic reticulum, pinocytotic vesicles, and intercellular modifications such as tight junctions. Furthermore, these cells undergo rapid shape change after treatment with thrombin and less extensive morphological changes following treatment with epinephrine, ADP and endotoxin. Of particular significance is that the cultured endothelial cells have fibrinolytic activity and contractile protein immunology indistinguishable from platelet thrombosthenin.

Endocrinology

Chertow BS, Buchanan WE, Mayrom MS, Schwartz TB: Hormonal modification of mouse liver lysosomal protein metabolism by cortisone acetate. *Endocrinology 92:722, 1973*

The effect of cortisone acetate (CA) on hepatic lysosomal protein metabolism and its relation to stabilization of the lysosomal membrane were studied in mice. Denatured Iodinated (^{125}I) Human Serum Albumin (IHSA) was injected by tail vein, and large granule fractions containing lysosomes were isolated and incubated at pH 7 and 37°C for one hour in room air. The uptake of IHSA was determined by measuring the total counts

present in the lysosomal fractions, and degradation was determined by measuring the TCA-soluble counts present immediately after sacrifice and released during incubation. Mice pretreated with a single injection of CA, 5 mg ip, two hours prior to sacrifice showed no significant change in uptake or degradation of IHSA. Mice pretreated with CA, 5 mg ip in three equally spaced injections the day before and two hours prior to sacrifice showed a 32 percent increase in degradation *in vitro*. Mice pretreated with CA, 5 mg ip daily for four days showed a 23 percent increase in degradation *in vitro*, 29 percent increase in degradation *in vivo*, and 73 percent increase in IHSA uptake. Although vitamin A, a lysosomal disrupting agent, decreased IHSA degradation, CA did not antagonize the effect of vitamin A. Hydrocortizone, 3.6×10^{-3}M *in vitro*, did not increase IHSA breakdown. CA did not decrease the nonsedimentable catheptic activity determined immediately after sacrifice. Thus a catabolic effect of CA on mouse liver protein metabolism is mediated through the lysosome, but, contrary to a generally held view, is not associated with membrane stabilization, although the integrity of the lysosomal membrane is necessary for optimal lysosomal catheptic activity.

Kornel L: Possible relationship of the derangement in corticosteroid metabolism to the etiological mechanism of essential hypertension. *Fed Proc 33:360, 1974*

The results of our previous studies on corticosteroid metabolism in normotensive subjects (N) and patients with essential hypertension (H) provided evidence for a decreased activity of cortisol $\triangle^4$-*hydrogenase*, and increased (presumably compensatorily) activities of cortisol 20-reductase and 6-hydroxylase in H. These results have been now confirmed in a larger number of patients (20 H, 20 N). A.M. and P.M. plasma levels of cortisol (F) were also determined in these subjects: they were found not to differ significantly between N and H. Since a derangement in metabolism of aldosterone (Aldo), analogous to that found by us in metabolism of F, was found recently in H by Genest and coworkers, but plasma levels of Aldo were elevated in these patients, we deduce the following: As a result of an overall decrease in activity of hepatic corticosteroid $\triangle^4$-hydrogenase in H, there is an elevation of plasma levels of those steroids for which negative feedback mechanism is complex and not controlled directly by plasma levels of these steroids (Aldo and possibly other mineralocorticoids); whereas, plasma levels of steroids controlling directly the release of the pertinent trophic hormone (cortisol→ACTH) are within normal range. Furthermore, there is in H a partial compensatory increase in production rates of metabolites non-reduced in ring A. The elevated plasma levels of Aldo and/or the other metabolites may be contributory to the production of hypertension.

Merkel FK, Ryan WG, Armbruster K, Seim SK, Ing TS: Pancreatic transplantation for diabetes mellitus: a case report. *Ill Med J 144:477, 1973*

Despite the use of exogenous insulin, the vasculopathy of juvenile diabetes remains a problem without a satisfactory solution. Diabetic angiopathy remains the third leading cause of blindness in the United States today. Nearly 20 percent of deaths attributable to diabetes are a result of diabetic glomerulosclerosis. Clearly, new approaches are necessary. Pancreatic allotransplantation is now being employed at Rush-Presbyterian-St. Luke's Medical Center, Chicago, for patients with severe diabetic retinopathy or nephropathy in an attempt to more satisfactorily correct the metabolic disorder. The body and tail of a pancreas is transplanted as an auxiliary allograft to the recipient groin, and the duct is anastomosed end-to-side to the recipient ureter. The function of the graft can be determined by measuring urine amylase values or blood sugar and blood insulin levels. Only by clinical trials can it be determined whether or not correction of the metabolic disorder by this method can prevent these vascular complications.

Northrop G, Ryan WG, Schwartz TB: Propranolol-induced insulin release in isolated rat islets of Langerhans. *Diabetes 22:91, 1973*

Immunoreactive insulin was measured in the medium following incubation of isolated rat islets of Langerhans in different concentrations of propranolol and propranolol plus glucose. Pretreatment with propranolol (20 μg/ml) prevented glucose (2 mg/ml)-mediated insulin release. Propranolol alone in concentrations up to 25 μg/ml did not cause insulin release; however, at 50 μg/ml this drug had strong beta-cytotrophic activity.

Hematology

Cole E, Curry A, Bachmann F: Post-operative increase of a circulating coagulation inhibitor (PIVKA) in open heart surgical patients. *Proc 4th Int Cong Thrombosis and Haemostasis, Vienna, 1973*

PIVKA (Protein In Vitamin K Absence) probably is a precursor of vitamin K dependent factors II, VII, IX and X and acts as a competitive inhibitor in the coagulation system. Patients receiving vitamin K antagonist drugs or with vitamin K deficiency exhibit this inhibitor in their plasma. A new protein band in the $BaSO_4$ eluate of plasma of vitamin K deficient rats has been reported. Low activity one-stage prothrombin times but normal or only slightly decreased levels of factors II, V, VII and X were often observed in patients who underwent open heart surgery with extracorporeal circulation, and the plasmas of these patients showed the presence of a PIVKA-type inhibitor. Complete coagulation screening profiles including PTT, PT, assays for PIVKA and factors I, II, V, VII and X, SGOT, and LDH and acrylamide gel electrophoresis of a concentrate of the vitamin K dependent factors were performed pre- and post-operatively in 13 patients undergoing open heart surgery. In all of these patients, there was an increase of an abnormal protein band visualized in acrylamide gels. This band was indistinguishable from that seen in patients receiving sodium warfarin or with vitamin K deficiency. Post-operative increases of PIVKA inhibitor activity; SGOT and LDH were statistically significant with a positive correlation between PIVKA inhibitor activity, SGOT and LDH were statistically significant with a positive correlation between PIVKA and LDH increases at the $p<0.001$ level. These studies suggest that this abnormal protein is probably released from the liver during extracorporeal circulation and decreased hepatic perfusion, and its presence in the circulation may be one of the causes of post-operative bleeding in the open heart surgical patient.

Frischer H, Carson PE, Bowman JE, Rieckmann KH: Visual test for erythrocytic glucose-6-phosphate dehydrogenase, 6-phosphogluconic dehydrogenase, and glutathione reductase deficiencies. *J Lab Clin Med 81:613, 1973*

A simple visual test has been developed to detect and distinguish erythrocytic glucose-6-phosphate dehydrogenase (G6PD), 6-phospho-gluconic dehydrogenase (6PGD), and glutathione reductase (GSSG-R) deficiencies either singly or in combination. The test is based on the non-enzymatic reduction of 2, 6, dichlorophenolindophenol by reduced glutathione which is generated from GSSG by GSSG-R if this enzyme is active and provided with NADPH either via G6PD or via 6PGD. Packed or sedimented erythrocytes are hemolyzed and the hemolysate is distributed and incubated into two tubes whose colors are observed. Initial standardization was achieved by using erythrocytes from individuals known to have normal or low G6PD, 6PGD, and GSSG-R activities. Diagnostic specificity was established and compared with that of cyanmethemoglobin elution. Normal erythrocytes require both NADPH generating steps of the pentose phosphate pathway for maximal redox-stimulated methemoglobin reduction; intermediate G6PD deficiency and complete 6PGD defiiciency are indistinguishable by tests based on methemoglobin reduction.

Fried W, Husseini S, Gregory S, Knospe WH, Trobaugh FE Jr: Effect of Cyclophosphamide on the hematopoietic microenvironmental factors which influence hematopoietic stem cell proliferation. *Cell Tissue Kinet 6:155, 1973*

Transplanted hematopoietic stem cells (HSC) regenerate more rapidly in the femoral marow of lethally irradiated hosts pretreated with cyclophosphamide (CY) four days prior to x-irradiation than they do in that of uninjected irradiated hosts (control). On the other hand, regeneration of HSC transplanted into irradiated hosts given CY seven days before x-irradiation is slower than in controls.

The microenvironment in the femoral marrow was studied at various times after giving CY. Four days after injecting CY, the number of colony-forming units (CFU), total nucleated hematopoietic cells, and mature myeloid and erythroid cells in the femoral marrow is still reduced, the total nucleated cell count is back to normal, but the number of mature myeloid elements in the marrow are significantly increased. These observations suggest the conclusion that the rate of proliferation of HSC is modulated by the number of mature myeloid cells in the microenvironment.

Fried W, Husseini S, Knospe WH, Trobaugh FE Jr: Studies on the source of hematopoietic tissue in the marrow of subcutaneously implanted femurs. *Exp Hemat 1:29, 1973*

The karotypes of dividing cells in femurs from CBA/Ca mice implanted into CBA/T6T6 hosts were determined, as well as karyotypes of cells in spleen colonies formed by transplanting suspensions of cells from these implanted femoral marrows. About 70 percent of the cells and of the CFU in the implants were of host type. However, if the implanted femurs were obtained from irradiated donors, all cells mitosing in the implant were of host origin. These results suggest that femoral marrow contains a relatively radioresistant cell population which is essential for supporting hematopoietic stem cell growth, but which is distinct from and does not differentiate into hematopoietic stem cells.

Frischer H, Bowman JE, Carson PE, Rieckmann KH, Willerson D Jr, Colwell EJ: Erythrocytic glutathione reductase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconic dehydrogenase deficiencies in populations of the United States, South Vietnam, Iran, and Ethiopia. *J Lab Clin Med 81:603, 1973*

The prevalence of erythrocytic glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconic dehydrogenase (6PGD), and glutathione reductase (GSSG-R) deficiencies was ascertained by a new visual test in 3,159 apparently healthy, unrelated individuals from the United States, South Vietnam, Iran, and Ethiopia. The reliability of the test was documented by comparison with starch gel electrophoresis for G6PD and 6PGD and with a series of assays for the three enzymes. Fully expressed G6PD deficiency was found in 10.6, 0.0, 4.1, 9.8, and 0.5 percent Afro-American, European-American, South Vietnamese, Iranian, and Ethiopian men, respectively. Partially G6PD-deficient men were found in all populations except in Afro-Americans; among 328 European-American men, the one with partial G6PD deficiency had an electrophoretically slow G6PD variant in erythrocytes and leukocytes. A so far unique instance of hemizygous G6PD deficiency combined with low GSSG-R was detected in an Afro-American man. The prevalence of decreased erythrocytic GSSG-R activity, either on an environmental or genetic basis was unrelated to sex and far greater than heretofore considered. Levels of decreased GSSG-R activity found in 0.3 percent of European-Americans and in 1.9 percent of Afro-Americans were observed in 7.3, 14.6, and 22.0 percent of Ethiopians, Iranians, and South Vietnamese. Erythrocytic GSSG-R activity is normally partially inhibited, and decreased GSSG-R activity can not only reflect mutational alerations of the apoprotein and riboflavin deprivation but also metabolic disturbances which enhance the degree of inhibition of the enzyme.

Knospe WH, Gregory SA, Fried W, Trobaugh FE Jr: Stimulation of hematopoiesis by femoral marrow curettage in sublethally irradiated mice. *Blood 41:519, 1973*

Femoral bone marrow curettage produced an intense stimulus on hematopoietic stem cells (HSC) in sublethally irradiated mice four days after curettage. A similar but lesser stimulation of ^{59}Fe incorporation into spleen and red cells was observed. Previous investigations have shown that this effect is not observed in unirradiated mice. Histologic studies of the curetted femurs indicated a rapid regeneration of a primitive mesenchymal tissue within the medullary cavities during the period of stimulation. It is suggested that the primitive mesenchymal cells synthesize a humoral factor that is capable of stimulating HSC in a marrow microenvironment of depleted cellularity. The observations are consistent with a hypothesis of inhibition of HSC response to a similar stimulus in a normocellular marrow by a mechanism of cell-cell interaction. The humoral factor affects HSC similar to fetuin, spleen extract, and alpha globulin fractions.

Knospe WH, Gregory SA, Fried W, Trobaugh FE Jr: Stimulation of hematopoiesis by marrow curretage in sublethally irradiated mice. *Proc 15th Ann Mtg Am Soc Hemat, Abstract p. 109, 1972*

The hypothesis that regenerating primitive marrow reticular cells produce a myelopoietic stimulatory factor was studied. Immediately after mice received 200R whole body irradiation, the right femoral marrows of half of them were curetted; sham curettage was performed in the other half. Four days later, the number of CFU in the left femoral marrow was assayed by the spleen colony technique. Two, four, and six days later, erythropoiesis in other mice was assayed by measuring the uptake of i.v. ^{59}Fe at four hours in the spleen and left femoral marrow, and at 24 hours in the rbc. There was a 3 to 6 fold increase in the marrow CFU of the animals treated with curettage and a similar but lesser increase in the uptake of iron ^{59}Fe by the spleen and rbc of the mice treated with curettage. Histologic study of the curetted femoral cavity indicated a marked regeneration of a primitive reticular tissue within the cavity; this tissue resembled fetal marrow. These results are compatible with the hypothesis that primitive reticular cells secrete a growth factor which stimulates the proliferation of hematopoietic stem cells (HSC) and the factor may be an alpha globulin. The stimulating effects on HSC are similar to the effects produced by the injection of fetuin or splenic extracts into sublethally irradiated mice. The results of all of these experiments are discussed relative to the role of alpha globulins as mitotic stimulators.

Rubinstein AS, Trobaugh FE Jr, Conti SA, Dansbie M: Ultrastructure of presumptive hematopoietic stem cells. *Blood 42:61, 1973*

The repopulating potential of bone marrow cells that have been subjected either to cryoprotective or to cryodestructive treatments were assayed by the spleen colony technique. There were four treatments. For each treatment group the ultrastructure of aliquots of the cell suspensions was studied, and an attempt was made to identify the cells responsible for hematopoietic repopulation. The repopulating potential of fresh glycerolized cells was greater than that of slowly cooled glycerolized cells, and both repopulating potentials were far greater than that of rapidly cooled glycerolized cells. With the exception of one cell type that was constantly well preserved, fresh glycerolized cells and cells frozen at controlled rates showed morphologic disruption. This type of cell was not found in suspensions of bone marrow cells that had been frozen rapidly, and it is proposed that it is the hematopoietic stem cell (presumptive stem cell of PSC). Two observations support the hypothesis that these cells are responsible for effecting hematopoietic repopulation of lethally irradiated mice injected with suspensions of marrow cells frozen to preserve their repopulating potential: (1) They are the only intact cells found in cryopreserved suspensions of marrow cells that effect hematopoietic repopulation. (2) They are not present in suspensions of marrow cells frozen so as to destroy the hematopoietic-repopulating potential.

Rieckmann KH, Willerson WD, Carson PE, Frischer H: Effects of tetracycline against drug-resistant *falciparum* malaria. *From Basic Research in Malaria, Special Issue, Proc Helminthological Society of Washington 39:339, 1972*

The effects of tetracycline against the Vietnam (Marks) and the Cambodia (Buchanan) strains of *Plasmodium falciparum* were determined in 37 non-immune volunteers. In 31 volunteers, tetracycline was given, in conjunction with a three-day course of amodiaquine or quinine, during an acute attack of malaria. Administration of tetracycline for 10 days cured 21 out of 22 infections, and administration of the drug for seven days cured six out of nine infections. In six volunteers, the first dose of a four-day course of tetracycline was given a few hours after the men had been bitten by infective mosquitoes. They were all protected against malaria. The findings indicate that tetracycline has a marked blood schizontocidal and causal prophylactic activity against two chloroquine-resistant strains of *P. falciparum.*

Trobaugh FE Jr, Bacus JW: Automated leukocyte classification by digital image processing. II. Development and testing of working laboratory model. *Proc 14th Intl Cong of Hematology, Sao Paulo, Brazil, July 16, 1972, Abstr No. 48*

Following the development of the theory presented in another paper, a working laboratory model of a machine which would classify leukocytes by digital image processing was developed. Some of the general design requirements were defined as follows: 1. There should be operator interaction. The operator would position the stained slide on the stage of the machine, make the initial focusing and screen the slide for erythrocyte and platelet abnormalities. 2. The machine should then automatically locate and classify 100 leukocytes in one (1) minute. 3. Classification criteria would utilize color as well as shape and density and other information. 4. Six (6) standard leukocyte types, segmented forms, band forms, lymphocytes, monocytes, eosinophils and basophils would be classified. 5. Abnormal cells would be detected and slides containing them, flagged so as to permit detailed examination by hematology technicians. During the development many problems were encountered, one of the most critical being the preparation of uniformly acceptable monolayer films of blood cells on the glass slides. This was solved by using a centrifugal technique. Machine performance as specified in the design requirements is discussed and detailed data presented. In summary, in the time stated, the machine will perform a one-hundred-cell differential, classify the six cell types, and detect abnormal cells. A three-minute motion picture showing the machine in action is available.

Trobaugh FE Jr, Chamberlain W, Husseini, Knopse WH, Fried W: A model for the study of stromal factors in hematopoiesis. *Proc 14th Intl Cong Hematology at Sao Paulo, Brazil, Jul. 1972. Abstr p. 13*

The S11S1D mutation in mice effects a congenital anemia which is not corrected by the transplantation of non-mutant (++) marrow cells, but is corrected by the implantation of several ++ spleens. An explanation for this phenomenon was sought. One quarter of a spleen from a ++ mouse and from an S1S1D mouse and one femur, with both ends removed, from a ++ mouse and one from an S1S1D mouse were transplanted subcutaneously into ++ and SS1S1D recipients. Eight weeks later the 6 hour uptake of 2 ucie Fe^{59} by the implants was measured, the histology of the implants studied and the number of colony forming units (CFU) in some of the femoral implants assayed. In the S1S1D hosts, ++ marrow and spleen implants incorporated four to five times more Fe^{59} than did the corresponding S1S1D implants. In ++ hosts, the ++ implants incorporated twice as much Fe^{59} as did the SS1S1D implants. Presumably the implants were more active when implanted in S1S1D animals because of the greater erythropoietic stimulus in the anemic hosts. The marrows of the ++ femoral implants each contained 300 to 400 CFU whereas the S1S1D implants contained only 5 to 40. The ++ implants throughout were more cellular and had more erythroid, myeloid and megakaryocytic cells than did the S1S1D implants. These studies indicate that the hematopoietic defect

of S1S1D mice lies in the hemotapoietic stroma which apparently lacks a factor essential for proliferation of hematopoietic stem cells, and implantation of nonmutant hematopietic stromal tissue corrects the defect. This model provides a reproducible means of studying the characteristics of this stromal defect.

Trobaugh F Jr, Husseini S: Effects of radiation on hematopoietic tissue. *Amer J Med Tech 39:119, 1973*

Hematopoietic tissue is characterized by a rapid rate of cell renewal which constantly replenishes the functional non-dividing cells of the blood. This cell renewal system starts with a reservoir of undifferentiated procursor cells, hematopoietic stem cells, which constantly feeds differentiated procursor cells into the dividing and maturing pool of the bone marrow while maintaining the numbers of stem cells.

Radiation damages the hematopoietic system by killing stem cells. These cells are highly radiosensitive whereas mature functional blood cells are radioresistant.

Following sublethal radiation, colonies of proliferating hematopoietic cells develop from endogenous stem cells.

Animals can be protected from lethal radiation by transplantation of suspensions of hematopoietic cells from other animals. Such transplantation can be effective if the immune reaction between the host's cells and the graft's cells can be avoided or controlled.

Willerson WD, Rieckman KH, Carson PE, Frischer H: Effects of minocycline against chloroquine-resistant falciparum malaria. *Am J Trop Med Hyg 21:857, 1972*

The antimalarial effects of minocycline, a semi-synthetic tetracycline, were evaluated in chloroquine-resistant *Plasmodium falciparum* infections. Nine volunteers infected with the Vietnam (Marks) strain were cured after each received a seven-day course of minocycline. Two additional subects infected with the same Vietnamese strain were cured after each received a combination of minocycline and quinine. Minocycline protected 16 of 18 volunteers after challenge with *Anopheles stephensi* mosquitoes infected with chloroquine-resistant strains of *P. falciparum*. Eleven men were protected against a single challenge by mosquitoes infected with the Cambodia (Buchanan) strain. Five of seven volunteers were protected against a single challenge by mosquitoes infected with the Vietnam (Marks) strain. No sporontocidal or gametocytocidal effects occurred in one volunteer who received a seven-day course of minocycline.

Infectious Disease

Devetski, RL: Primary cutaneous mycobacteriosis. *J Indiana State Med Assoc, Nov. 1972, pp. 1149-1151*

We have detailed a case of primary cutaneous tuberculosis occurring in a laboratory technician. The specific presentation was unusual in that the lesion had initially responded to conventional therapy; but the subject returned several months later with a healed "primary lesion," then associated with rather malignant-appearing nodes in the epitrochlear and axillary areas of the involved arm. The emphasis should be quite logically directed toward the importance of an adequate history prior to treatment, as well as continued awareness of the multiplicity of presenting forms for active tuberculosis.

Nephrology

Armbruster KFW, Ing TS, Kark RM: Nondialytic treatment of chronic renal insufficiency. *Ration Drug Ther 5:1, 1973*

The conservative therapy of patients with chronic renal insufficiency in the areas of water, electrolytes, protein and caloric intakes is discussed. In addition, treatment of complications of chronic renal failure are described.

Eybel CE, Armbruster KFW, Ing TS: Skin pigmentation and acute renal failure in a patient receiving phenazopyridine therapy. *JAMA 228:1027, 1974*

Pigmentation of the skin and of urinary casts as well as acute renal failure occurred in a patient receiving phenazopyridine therapy. Whether the acute renal failure was related to the therapy was uncertain. The cutaneous pigmentation was believed to be secondary to drug accumulation as the result of reduced renal excretion.

Ing TS, Kovithavongs T, Pichairut O, Bachmann F: Blood coagulation abnormalities in patients with chronic renal failure. *Proc 5th Int Cong Nephrol, Mexico City, 1972*

Extensive blood coagulation studies in 11 patients treated with maintenance hemodialysis revealed significantly more abnormalities than in nine patients with renal allografts both on and off sodium warfarin. In the dialysis group, 54 percent had a short partial thromboplastin time (PTT) and an elevated level of fibrin degradation products (FDP) and 100 percent, an abnormal fibrinogen immunoelectrophoresis (FIE). One patient had cryofibrinogen while another, abnormal protamine sulfate dilution test. In the non-anticoagulated transplant recipients, 11 percent had a reduced PTT; 42 percent, an elevated level of FDP; and 25 percent, an abnormal FIE. In the anticoagulated transplant patients, coagulation abnormalities were found mainly in those who still had their own kidneys or those who showed rejection phenomenon.

Our data suggest that coagulation abnormalities are found in a significant number of patients with chronic renal failure. These findings are consistent with activation of the coagulation mechanism and the conversion of a small fraction of normal fibrinogen into fibrin monomer and/or fibrinogen derivatives. Successful renal transplantation results in a significant improvement of these abnormalities.

Meites HL, Ing TS, Kovithavongs T, Economou SG: Femorasaphenous fistula for maintenance hemodialysis. *Can J Surg 16:335, 1973*

A new method for constructing an internal arteriovenous fistula for maintenance hemodiaysis utilizes the femoral artery and the long saphenous vein. The vein is divided at the saphenofemoral junction and the proximal valves within it, and the proximal branches from it are removed. The proximal end of the vein is anastomosed end-to-side to the artery and the vein itself then placed in a subcutaneous position. In the three functioning fistulas we have constructed, flow rates have been satisfactory and there has been no evidence of cardiac decompression.

Shepherd RL, Ing TS, Magalhaes R, Economou SG: Cervical arteriovenous fistulae for maintenance hemodialysis: A new technique. *Nephron (Basel) 11:7, 1973*

Four patients with a paucity of peripheral veins had cervical arteriovenous fistulae created, utilizing the external jugular vein and either the superior thyroid artery or the external carotid artery. The fistulae provided a reasonably adequate solution for maintenance hemodialysis in these patients with chronic renal failure.

Wang G, Pillay VKG, Ing TS, Armbruster KFW, Rosenberg JC: Ascites in patients treated with maintenance hemodialysis. *Nephron (Basel) 12:105, 1974*

Eight patients treated with maintenance hemodialysis developed significant ascites. Fluid retention appears to be a common denominator. Increased capillary permeability from uremia may be a contributory factor. Compartmentalization of ascitic and nonascitic fluids is often observed. Therapeutic measures include fluid and sodium restriction, fluid

removal by dialysis, abdominal paracentesis, intravenous infusion of ascitic fluid or albumin and renal transplantation. The latter appears to be the ideal therapy.

Wu BC, Pillay VKG, Hawker CD, Armbruster KFW, Shapiro HS, Ing TS: Hypercalcaemia in acute renal failure of acute alcoholic rhabdomyolysis. *S Afr Med J 46:1631, 1972*

A case of acute alcoholic rhabdomyolysis with acute renal failure and transient hypercalcaemia during the recovery phase of the renal dysfunction, is described. Possible causes for the hypercalcaemia include secondary hyperparathyroidism and resorption of calcium from recovering muscle.

Neurosurgery

Norton T, Paul RP: The Arnold-Chiari deformity in elderly patients: Diagnosis and treatment. *Neurochirurgia 15:153, 1972*

Arnold-Chiari deformities occur in elderly patients more frequently than is generally thought. Such patients commonly manifest clinical symptoms of paraplegia, vertical nystagmus, and loss of corneal and gag reflexes. The deformity thus mimics other disorders of the cranio-vertebral junction, such as foramen magnum neoplasms.

Diagnostic contrast studies clearly define Arnold-Chiari deformities, particularly angiography, which demonstrates a caudally displaced confluens sinuum and low-set lateral sinuses. Myleography or cervical manipulation, however, are often accompanied by respiratory embarrassment and may be avoided if the clinical condition is recognized.

Selby RC, Lopes NM: Torulomas (cryptococcal granulomata) of the central nervous system. *J Neurosurg 38:40, 1973*

Three new cases of cryptococcal granuloma of the central nervous system are reported and compared with 37 previously described cases. The lesion may appear with or without evidence of meningitis. Resection of the granuloma followed by prophylactic or therapeutic chemography is recommended as the treatment of choice. Serial lumbar punctures and blood and CSF antigen levels are of value in determining response to treatment.

Selby RC, Pillay KV: Osteomyelitis and disc infection secondary to *Pseudomonas aeruginosa* in heroin addiction. *J Neurosurg 37:463, 1972*

Two cases of osteomyelitis of the spine caused by *Pseudomonas aeruginosa* are described. The organism apparently was introduced by contaminated syringes or needles used by heroin addicts. This organism and the pathology should be kept in mind in patients known to have been heroin addicts and who are suffering from spinal problems, especially if there is evidence of infection.

Whisler WW, Hill BJ: A simplified technique for injection of the Gasserian ganglion, using the fluoroscope for localization. *Neurochirugia 5:167, 1972*

A fluoroscopic technique is described for rapidly and easily locating the foramen ovale and injecting the Gasserian ganglion in the treatment of tic douloureux. The results of 35 patients are discussed. There were six complications which consisted of three patients with complete analgesia and loss of the corneal reflex and three patients with paralysis of the motor division of the trigeminal nerve. Other side effects and observations are also discussed.

Pediatrics

Shakibi JG, Diehl AM: Postnatal development of the heart in normal Swiss-Webster Mice. *Lab Anim Sci 22:668, 1972*

The hearts of 140 normal newborn Swiss-Webster mice were examined by serial section, and two were found to have congenital heart disease. The cardiovascular anomalies consisted of single cases, one lacking a tricuspid valve and one with a ventricular septal defect. The heart of the newborn Swiss-Webster mouse develops further after birth. The septal cusp of the tricuspid valve and the membranous portion of the ventricular septum are formed after birth, and valvulae venosae are resorbed in the first week of extrauterine life.

Psychiatry

Berger JC: Suicide attempts related to congenital facial deformities: Two unusual case reports. *Plast Reconstr Surg 51:323, 1973*

The discrepancy between the anticipated rate of depression and suicide in patients with congenital cleft lip and cleft palate deformities, compared to the actual statistical rate, is pointed out. A possible explanation for this discrepancy is oulined. Two rare cases of attempted suicides in adults with cleft lips and palates are reported.

Jones FDL, Maas JW, Dekirmenjian H, Fawcett JA: Urinary catecholamine metabolites during behavioral changes in a patient with manic-depressive cycles. *Science 179:300, 1973*

3-Methoxy-4-hydroxyphenylglycol and normetanephrine were analyzed in daily urine specimens of a patient with manic-depressive cycles who was studied longitudinally. The quantities of these catecholamine metabolites excreted into urine were decreased during periods of depression as compared with periods of mania. Urinary excretion of 3-methoxy-4-hydroxyphenylglycol varied cyclically with a period length of approximately 20 days. Changes in this metabolite, and perhaps in normetanephrine, preceded the affective and behavioral shifts.

Peters J: Towards a reductionist view of Sigmund Freud. *J Biol Psychol 15:24, 1973*

In recent years many people have attempted to propose highly philosophical interpretations of Freud's writings. This essay offers opposition to the above trend. Indeed, the author accents the possibility that Sigmund Freud never left a neurobiological framework as the ultimate basis for understanding the human mind. At the same time, however, the author recognizes that Freud's writings have many philosophical implications.

Surgery

Anderson OS, Jonasson O, Merkel FK: En bloc transplantation of pediatric kidneys into adult patients. *Arch Surg 108:35, 1974*

A technique is described for en bloc transplantation of both kidneys from pediatrc cadaver donors into adult recipients, whereby donor aorta is interposed into recipient external iliac artery. Three cases utilizing this technique are reported, and two of these patients currently survive with normal renal function. The operation is simple to perform, adaptable to a variety of situations, and can increase the pool of cadaver donors by making small pediatric donors available for adult recipients

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THE ROLE OF THE IMMUNE AFFERENT LIMB IN TUMOR CONTROL

Carleton C. Stewart
Carlos A. Perez
Barbara Wagner

ABSTRACT. The role of the afferent limb is considered in the initiation of immunity against a lymphosarcoma. The results suggest that a tumor-associated antigen is present on the Gardner 6C_3HED lymphosarcoma, which can effectively produce an immune response in C_3H mice. Interruption of the afferent limb by lymphadenectomy a short time before or after tumor inoculation impairs the initiation of immunity to this tumor. Results further suggest that sufficient numbers of tumor cells must reach the regional lymph node before immunity can be demonstrated, and that the mere presence of tumor cells in the tissues is an insufficient stimulus for the initiation of immunity.

INTRODUCTION

It has been shown[1-6] that initiation and expression of an immune response require at least three closely interrelated components: a) an afferent limb comprised of the lymphatic vessels draining the tissue, through which antigen flows to lymphoid tissues; b) lymphoid tissue, usually the regional lymph node, whose cells respond to the antigen by producing antibodies or antigen-sensitive effector lymphocytes; and c) an efferent limb which carries the antibody or the effector lymphocytes to the site of antigen deposit. Thus, an interruption of any one of the components is likely to result in impaired immunologic activity.

There is now a great deal of evidence to suggest that tumor cells can induce immune responses in their hosts and must, therefore, be antigenic.[7-9] Although in most instances the resulting immune response is inadequate to reject clinically apparent tumors, it may be that many neoplastic cell transformations occur throughout life but are immunologically recognized early enough to be rejected before clinical manifestations are apparent. The concept of immunosurveillance[10] suggests that cancer develops when immune responses are inadequate, or when transformed cells are not sufficiently antigenic to be recognized early. This latter consideration is most important, since it is likely that autochthonous tumor cells might express only weak antigenic determinants not easily recognized by the host's immune system.[11,12] Thus, an accumulation of tumor cells might be necessary before recognition by the immune system occurs. The response, once established, may compete ineffectively with the proliferation of tumor cells.

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Presented at Presbyterian-St. Luke's Hospital Cancer Center Seminar, Chicago, Illinois, December 14, 1973

Our main interest has been to investigate the level at which tumor cells become a sufficient antigenic stimulus to initiate an immune response, and the importance of the afferent limb to the response.

Demonstration of a tumor antigen

The $6C_3HED$ Gardner lymphosarcoma, a solid tumor well characterized by Powers et al.,[13] was used in these studies. Their work as well as our own[14] has suggested that this tumor can induce an immune response. A direct demonstration of a tumor-associated antigen was lacking, however, and further investigation seemed essential to prove that this tumor had a tumor-associated antigen.

Xenogeneic antitumor serum was prepared as previously described,[15] by injecting rabbits every two weeks for eight weeks with $6C_3HED$ tumor cells. Serum was absorbed with C_3H/Anf spleen lymphocytes to remove antibody directed against histocompatibility and lymphocyte antigens of the C_3H mouse.

The number of cells surviving treatment with antibody and complement was determined by measuring cell viability using the pronase-cetrimide technique.[15] Briefly, cells are treated with the proteolytic enzyme pronase to digest dead cells. The cytoplasm of the remaining viable cells is then lysed by the detergent cetrimide, liberating nuclei which are counted with an electronic particle counter. Cetrimide also eliminates non-nucleated cells (e.g. erythrocytes) and breaks up aggregates which might form by the agglutinating antibody.

The results of this study are shown in Fig. 1. After absorption of 5 ml antiserum with the cells from 20 or more mouse spleens (4×10^9 cells) all cytolytic activity against lymphocytes was removed. This absorbed antiserum retained considerable cytolytic activity against the $6C_3HED$ lymphosarcoma. The cytolytic activity was somewhat reduced by absorption with spleen lymphocytes but no further reduction in cytolytic titer was found when absorption with lymphocytes from more than 20 normal spleens was performed. The initial reduction in titer (up to 20 spleens) suggests that an antigen is shared by both spleen lymphocytes and tumor cells. Since

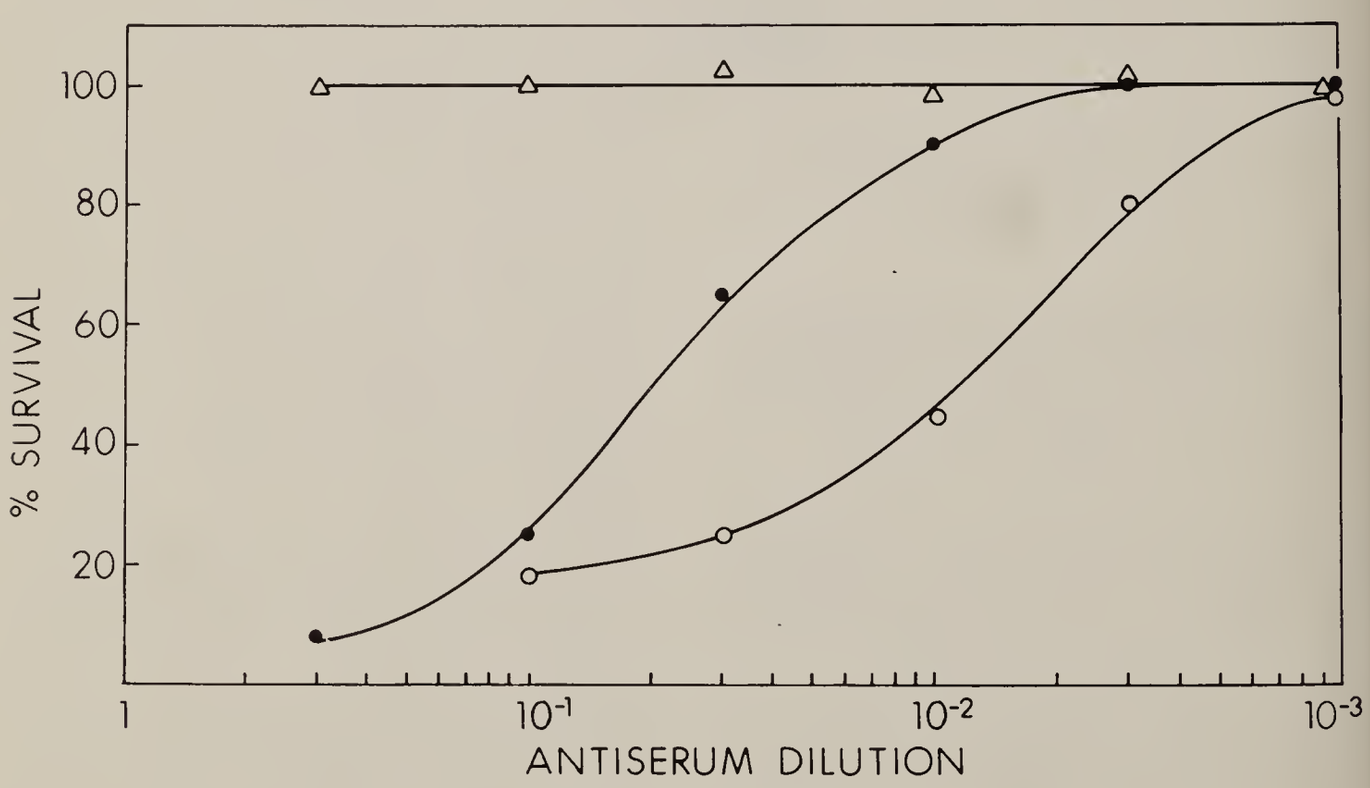

Fig. 1—Cytolytic activity of antilymphosarcoma serum. Lymphocytes from 20 or more spleens were used to absorb the antiserum. The open and closed circles show the activity against tumor cells of unabsorbed and absorbed serum respectively. The triangles show the activity of lymphocyte-absorbed serum against spleen lymphocytes.

absorption with lymphocytes did not remove cytolytic antibody for these tumor cells the data indicate the presence of a tumor-associated antigen.

In vivo immunization

To determine whether the lymphosarcoma cells were immunogenic to the host animals, tumor-bearing mice were cured by local irradiation and tested to determine whether they could reject a tumor-cell challenge. C_3H/Anf mice were injected with 10^6 tumor cells in the flank. Three days later a palpable tumor of about 5 mm diameter was locally irradiated with a single dose of 4000 rads (220 kvp, 15 ma, 2 mm copper). The animals were observed for 45 days and cured animals were then challenged with varying numbers of lymphosarcoma cells injected subcutaneously in the opposite flank.

Fig. 2 shows the results of these experiments. The cured animals exhibited a resistance to the proliferation of tumor cells not present in nonimmunized control mice, all of which developed tumors at every inoculum size. However, even cured animals were unable to effectively reject injections of 10^7 cells.

Role of the afferent lymphatics

In order to evaluate the role of the afferent limb of the immune response, regional lymphadenectomy was performed at different times before and after the injection of 10^6 tumor cells in the flank. In each group the animals were given local irradiation (4000 rads to the tumor three days after injection) and then observed for tumor recurrence. Fig. 3 shows the results of this experiment, which have also been described in more detail elsewhere.[16] Reduced cure rates were observed when

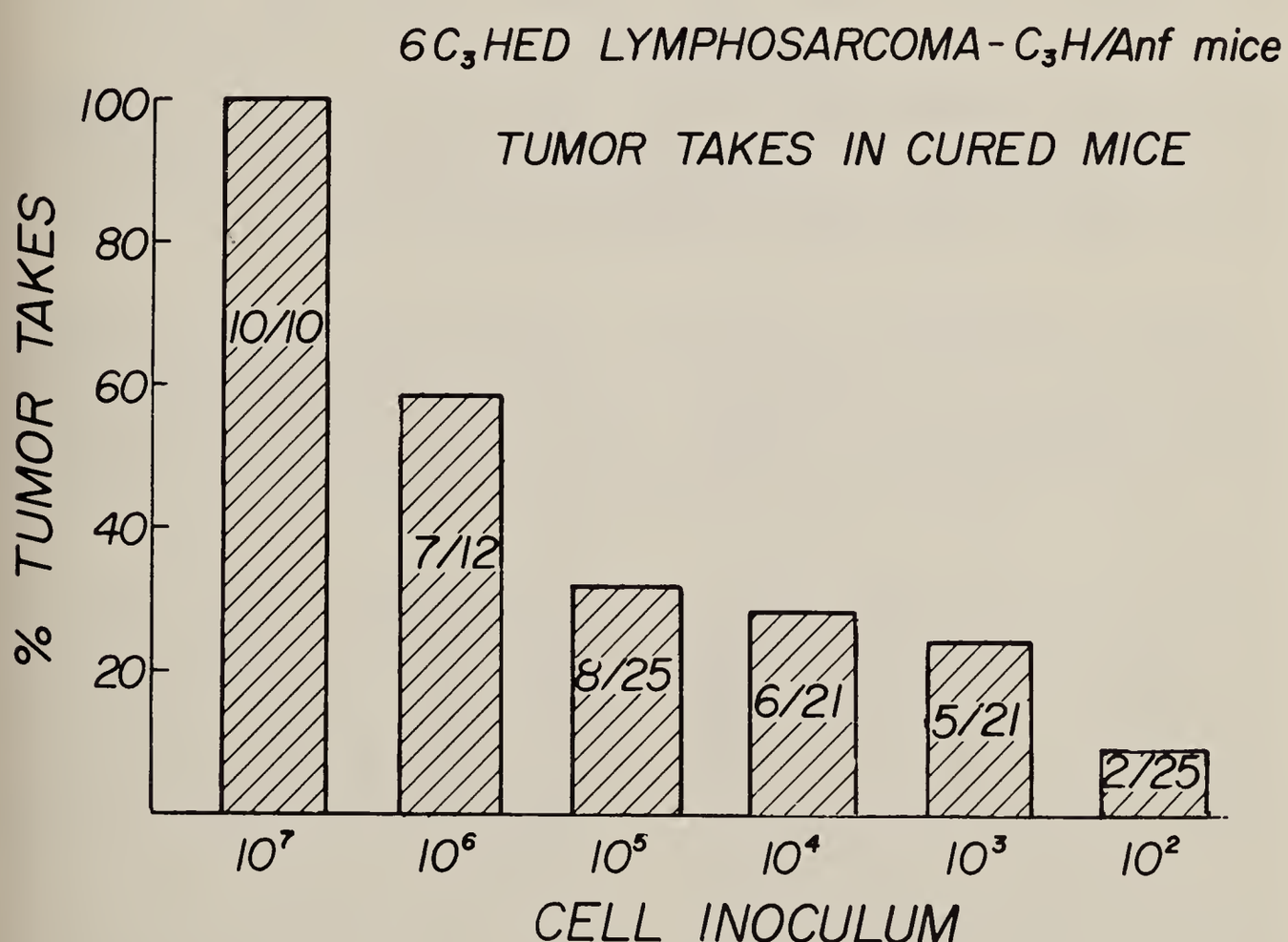

Fig. 2—Tumor occurrence in cured mice. Mice were given 4000 rads to the tumor three days after injection of 10^6 tumor cells. Tumor-free mice were challenged 45 days later with various cell inocula and the number of tumor takes observed. Control unirradiated mice had 100 percent tumor takes at all inoculum sizes except for 10^2 cells which was 80 percent.

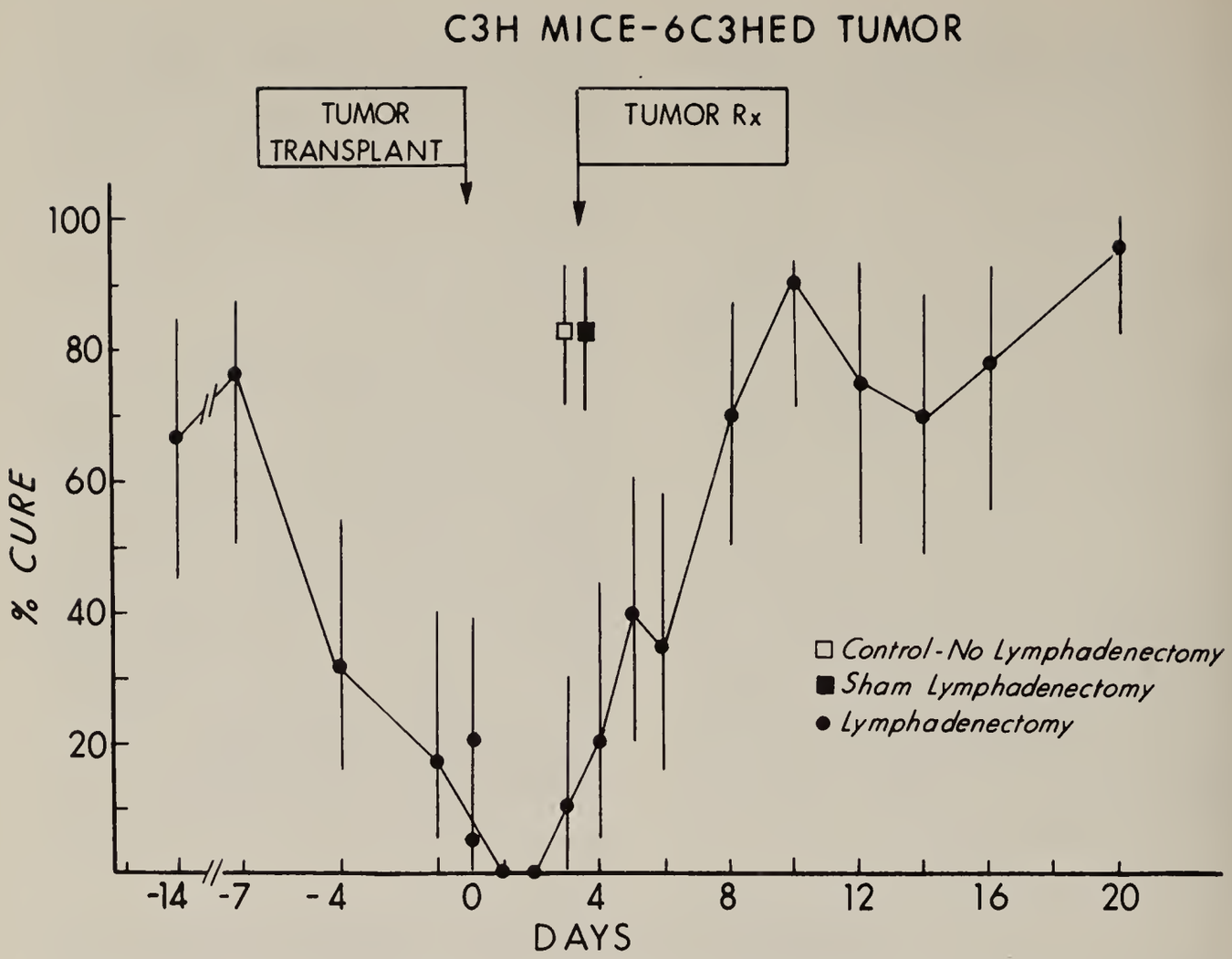

Fig. 3—Effect of lymphadenectomy on tumor cure. Regional axillary lymph nodes were surgically removed at various times before or after injection of 10^6 cells. The two points shown on day zero indicate the cure rate in mice lymphadenectomized just before or just after tumor cell injection. Three days later, the tumor-bearing flank was given a local dose of 4000 rads. Nodes and lymphatics were not dissected in mice that received sham lymphadenectomies. The vertical lines indicate the 95 percent confidence intervals. (From reference 14).

lymphadenectomy was done starting at four days prior to the tumor-cell injection. When lymphadenectomy was performed after tumor-cell injection, the cure rate reached a nadir on days 1 and 2 and then began to increase. After day 6 the cure rate did not differ from control values.

As early as 12 hours after injection, some of the anterior axillary lymph nodes were found on removal to contain tumor cells (Fig. 4). All nodes were assayed for viable malignant cells by transplanting them into untreated C_3H/Anf mice, and they contained tumor cells by day 6. However, when the primary growth in the flank was controlled by local tumor irradiation (day 3 after cell injection), the regional lymph nodes become negative (no viable tumor cells detected) seven days after injection of tumor cells.

Since mice whose lymph nodes contain viable tumor cells at the time of irradiation can be cured by local treatment which does not include the nodes, these nodal tumor cells are probably killed by a host-immunological response. When regional lymphadenectomy was performed near the time of tumor-cell injection, the immunological response was severely impaired, rendering the host unable to eliminate the residual cells outside the field of irradiation. One possible explanation for the cure kinetics shown in Fig. 3 is that when lymphadenectomy was performed 7 to 14 days prior to tumor-cell injection, time was sufficient for new lymphatics to be established to another regional node, and after six days following injection, an immune response sufficient to reject residual tumor cells had already been established, so that

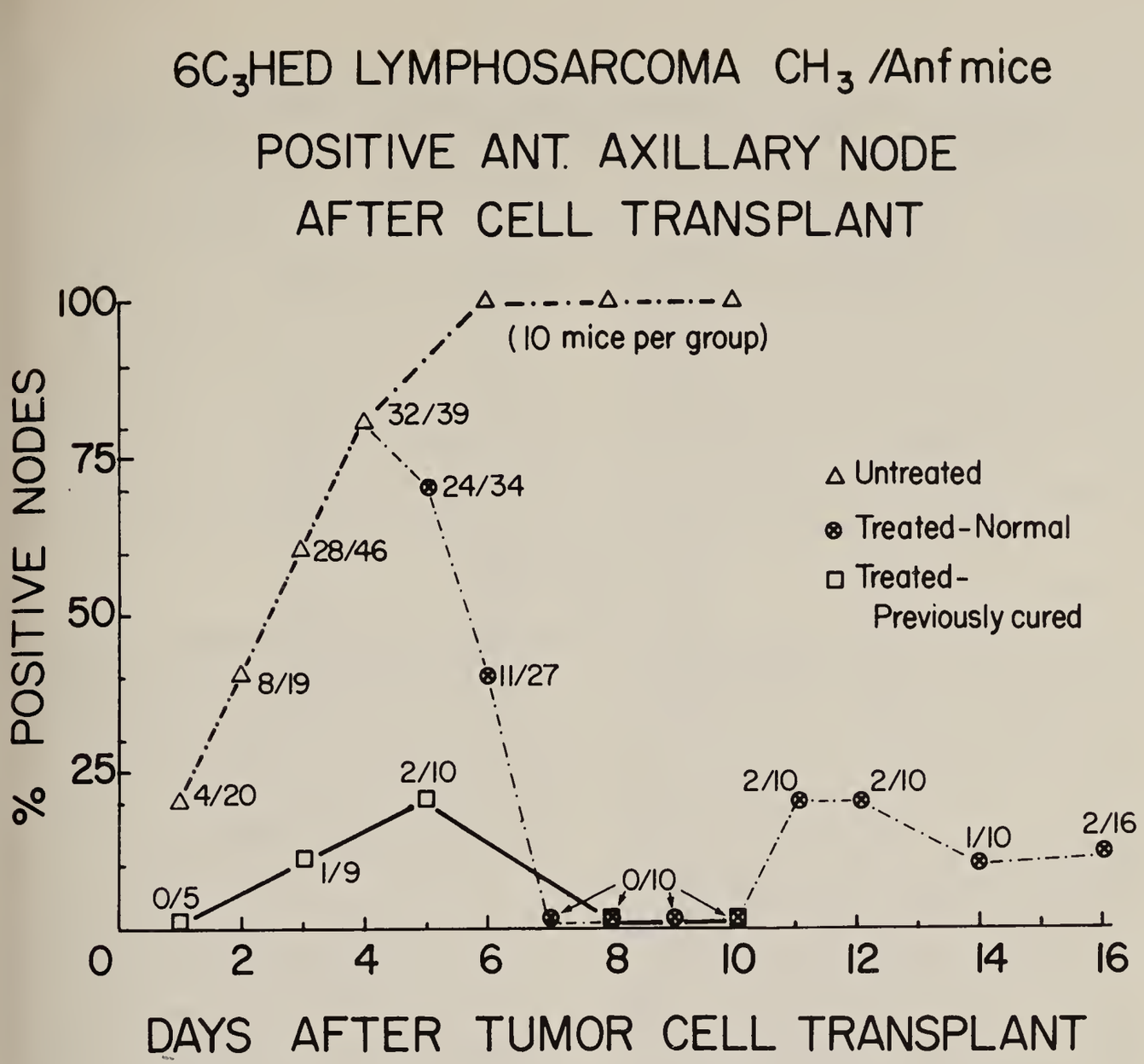

Fig. 4—Incidence of tumor cells in regional lymph nodes. Regional axillary lymp nodes were removed at various times after injection of 10^6 tumor cells in the flank and transplanted into the flank of normal recipients. The "Untreated" control group was not irradiated. The tumor bearing-flank of the "Treated-Normal" group was irradiated three days after injection. A third "Treated-Previously Cured" group of animals was irradiated three days after an initial injection of 10^6 cells and those which had not developed a tumor by 45 days were rechallenged on the opposite flank with 10^6 tumor cells. This second flank was then irradiated 3 days later and nodes were bioassayed as a function of time after the challenge injection. (From reference 17).

cure rates approached those among non-lymphadenectomized controls. Supporting evidence has been reported by Lambert et al.[1] who showed that at least four days are required to repair and produce collateral lymphatics draining a peripheral tissue.

Minimum cell number required for immunization

In order to further evaluate both the role of the afferent limb and the number of tumor cells required to produce immunity, animals were immunized and subsequently challenged with viable tumor cells. Mice were injected on the right flank with 10^6, 10^5, 10^4, or 10^3 tumor cells. Three days later the injection site was irradiated with a local dose of 4000 rads and this tumor was, in most cases, cured by the local irradiation. Either 1 or 10 days after the initial injection a challenge inoculum of 10^6, 10^4, or 10^2 viable tumor cells was introduced in the opposite flank. The results are shown in Table I. Tumors grew progressively at the site of the second injection if the challenge was given on

TABLE I

INCIDENCE OF TUMOR APPEARANCE AT PRIMARY SITE OF INJECTION OF MICE LOCALLY IRRADIATED WITH 4000 RADS AND CHALLENGED WITH A SECOND TUMOR CELL INJECTION ONE OR TEN DAYS FOLLOWING THE INITIAL INJECTION

No. Cells Primary Injection	No. Cells Challenge Injection	Day 1		Day 10	
		Primary	Challenge	Primary	Challenge
10^6	10^6	1/10	10/10	1/10	2/10 ($P < .01$)
	10^4	5/10	8/8	4/10	1/10 ($P < .01$)
	10^2	5/10	4/6	6/9	0/9 ($P < .05$)
10^5	10^6	0/10	10/10	2/10	10/10
	10^4	1/10	10/10	3/10	5/8
	10^2	0/10	7/10	0/8	6/8
10^4	10^6	0/8	8/8	0/7	7/7
	10^4	0/10	10/10	1/8	7/8
	10^2	0/8	8/8	0/5	4/5
10^3	10^6	0/10	10/10	0/10	10/10
	10^4	0/10	10/10	0/10	10/10
	10^2	0/9	9/9	0/9	4/9

day 1. In contrast, when the challenge was made on day 10, 80 percent of animals which had received an immunizing dose of 10^6 cells rejected the challenge inocula of the same size. Animals which received immunizing doses of fewer than 10^6 cells were unable to reject challenge inocula.

This data, coupled with the observation that no tumor cells were found in regional lymph nodes when 10^5 or fewer tumor cells were injected,[17] suggest that a sufficient number of tumor cells must reach the regional lymph node via the afferent limb before an immune response is initiated. Since regional lymphadenectomy immediately prior to or after injection with numbers of tumor cells sufficient to induce immunity also reduces the cure rate, it seems reasonable to believe that interruption of the afferent limb impairs sensitization and that the mere presence of tumor cells in the tissues is not adequate to induce an immune response. Even if an immune response is initiated, the number of tumor cells that can be rejected will depend upon the interaction of factors which tend to protect (e.g., blocking antibody or antigen-antibody complexes) or destroy tumor cells (e.g., cytotoxic effector lymphocytes).

Clinical evidence and implications

Recent papers report the presence of tumor-associated or specific antigens in such human neoplasms as carcinomas of the ovary and cervix,[18,19] sarcomas of soft tissues and bone,[20] Hodgkin's Disease,[21] and melanoma.[22] Furthermore, *in vitro* evidence of antibodies against the antigens in the serum of patients with cancer, as well as microtoxicity studies, point toward a correlation between clinical prognosis and the ability of the serum or the lymphoid cells of the hosts to destroy the tumor cells.[23] That the immune response may play a role in human neoplasms is suggested by a greater incidence of malignant tumors in patients with immuno-deficiency diseases.[24–27] A lower incidence of tumors in the normal population, possibly implying protection, has led to the concept of immunological surveillance as described by Burnett.[10] The occurrence of tumors, particularly those of a lympho-reticular origin, is also high in patients who undergo prolonged immunosuppression following organ transplantation.[28,29] It is likely that this increased occurrence is secondary to immune suppression induced by chemotherapy rather than a carcinogenic prop-

erty of any immune-suppressive agent used.[26] For these patients, the defect is most likely in the central lymphoid tissues.

While the effects just described would be expected to effect the central and afferent limbs of the immune response, the importance of the afferent limb becomes critical when regional lymph node dissection is considered during cancer treatment. It seems likely that when human neoplasia becomes clinically apparent, the tumor would have reached a sufficient size to have induced an immune response. Our studies suggest that regional lymphadenectomy would have no detrimental effect thereafter, (although Fisher et al.,[30] have suggested that regional nodes are important in maintaining immunity). When immunity has not been established either because tumor cells have not reached the regional node or because they are not sufficiently antigenic to have aroused an early response, the regional lymph node dissection and disruption of the afferent limb may interfere with the initiation of an immune response, an effect which might then compromise the patient's ability to cope with residual tumor cells.

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THORACOTOMY FOR BRONCHOGENIC CARCINOMA: 500 CONSECUTIVE PROCEDURES

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ABSTRACT. A series of 500 patients underwent thoracotomy for bronchogenic carcinoma between March, 1963 and January, 1972. Of the total, 175 patients (35 percent) received preoperative irradiation. The resection rate in both groups was essentially the same. Survival was determined by the life-table method and showed an overall five-year survival of 26 ± 5 percent and ten-year survival of 17 ± 6 percent. Of all patients receiving the same operation, there was no substantial difference in survival between the irradiated and non-irradiated groups, except for those receiving a lobectomy, where surgery-only patients did better. This could be attributed to more advanced disease in irradiated patients. With the exception of oat cell carcinoma, cell type had no influence on survival. Patients receiving a segmentectomy did as well as those having a lobectomy. It appears that routine preoperative irradiation for bronchogenic carcinoma offers no benefit.

INTRODUCTION

The results of surgery for bronchogenic carcinoma generally have been less favorable than for cancer in other sites, i.e., colon or breast. Much interest has been generated in the combination of preoperative irradiation with surgery,[1,2] and a collaborative study to determine the effectiveness of such an approach has recently been completed.[3]

A large collaborative study is able to collect a large quantity of patient data from many institutions serving several different patient populations. For this reason it was felt that a study of all patients operated upon by a single thoracic surgery service serving a given patient population, and comparing to larger collaborative studies when possible, would be worthwhile.

METHODS AND MATERIALS

The clinical material for this study was a series of 500 consecutive patients who underwent thoracotomy for bronchogenic carcinoma between March, 1962 and January, 1972. The patient population was drawn from both the University of Illinois Medical Center and the Rush-Presbyterian-St. Luke's Medical Center, both in the west side medical complex, Chicago. The operations were performed by a single thoracic surgery service which has been

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affiliated with both hospitals. The age/lung involvement/sex/cell-type distribution is shown in Table I, and followed those generally reported for this malignancy. All specimens were confirmed as malignant by pathologist's report.

Of the 500 total patients, 175 (35 percent) received preoperative irradiation, but not all at one of these hospitals, or all on a random basis. Many patients were selected for irradiation in order to render a marginally operable patient suitable for resection. The types of resections performed are listed in Table II. Survival data was determined by the life table method.[4]

TABLE I

PATIENT POPULATION STATISTICS

	Prior Irradiation	Surgery Only	Total
Average Age	60	62	61
Right Lung Involved	—	—	57%
Left Lung Involved	—	—	41%
Lung Not Specified	—	—	2%
Males	86%	79%	82%
Females	14%	21%	18%
Epidermoid Carcinoma	63%	52%	56%
Adenocarcinoma	13%	31%	25%
Oat Cell Carcinoma	10%	4%	6%
Unspecified Bronchogenic	13%	10%	11%
Other Cell Types	1%	3%	2%

TABLE II

RESECTIONS PERFORMED

Resection	Patient Group	Number	Percent of Patient Group
Rt. Pneumonectomy	TL(a)	52	10
	PI(b)	27	15
	SO(c)	25	8
Lt. Pneumonectomy	TL	71	14
	PI	30	17
	SO	41	13
Pneumonectomy with Trachael Sleeve	TL	18	4
	PI	17	10
	SO	1	0.3
Lobectomy	TL	232	46
	PI	70	40
	SO	162	50
Segmentectomy	TL	84	17
	PI	15	9
	SO	69	21
All Resections	TL	457	91(d)
	PI	159	91(d)
	SO	299	92(d)

(a) Total.
(b) Prior irradiation.
(c) Surgery only.
(d) Resection rate.

RESULTS

The survival for the series as a whole is given in Table III. The surgery-only group did better overall than the preoperative-irradiation group. However, the irradiated group received more extensive surgery; i.e., 42 percent having received a pneumonectomy as opposed to 21 percent of the non-irradiated group, and all but one of the tracheal sleeve resections were performed on irradiated patients. When the two groups are compared for the same procedure, as in Table IV, the survival difference vanishes for pneumonectomy and remains large for lobectomy. The difference also appears large for segmentectomy, but the small number of patients receiving irradiation prior to this resection makes this observation unreliable. Table IV also shows that patients on whom a segmentectomy was performed survived as long as those who received a lobectomy.

Table V illustrates survival for the most frequently encountered cell types, and Table VI shows the survival for a given operation with a given cell type. Cell type is seen to be of no prognostic value, except for oat cell which does much worse than the others. No substantial difference is seen with respect to irradiation except, again, in those patients who received a lobectomy.

DISCUSSION

The only survival difference found between irradiated and non-irradiated patients is in those who received a lobecto-

TABLE III

SURVIVAL FOR SERIES AS A WHOLE*

Interval	N = 500 All Patients	N = 175 Prior Irradiation	N = 325 Surgery Only
1 year	59 ± 2	45 ± 5	66 ± 3
3 year	33 ± 2	21 ± 3	41 ± 3
5 year	26 ± 2	15 ± 3	32 ± 3
7 year	23 ± 2	13 ± 3	29 ± 3
10 year	17 ± 3	10 ± 3	20 ± 4

*Numbers are percent ± standard error

TABLE IV

OPERATIVE MORTALITY AND FIVE-YEAR SURVIVAL FOR PROCEDURES PERFORMED*

Procedure	Patient Group	Number	Operative Mortality	Survival
All Pneumonectomy	TL(a)	141	13 ± 3	14 ± 3
	PI(b)	74	16 ± 4	12 ± 4
	SO(c)	67	9 ± 4	17 ± 5
All Lobectomy	TL	232	5 ± 2	33 ± 4
	PI	70	7 ± 3	21 ± 5
	SO	162	4 ± 2	39 ± 5
All Segmentectomy	TL	84	4 ± 2	36 ± 6
	PI	15(d)	0 ± 0	20 ± 12
	SO	69	4 ± 3	39 ± 7

(a) Total.
(b) Prior irradiation.
(c) Surgery only.
(d) Too few to be reliable.

*Mortality and survival as percent ± standard error.

TABLE V

SURVIVAL FOR THE MOST FREQUENTLY ENCOUNTERED CELL TYPES*

Cell Type	Number	Survival	Years
Epidermoid	281	28 ± 3	5
Adenocarcinoma	123	23 ± 5	5
Oat Cell	30	13 ± 6	2

*Survival as percent ± standard error.

TABLE VI

OPERATING MORTALITY AND FIVE-YEAR SURVIVAL FOR MOST FREQUENT PROCEDURES PERFORMED FOR MOST FREQUENT CELL TYPES

Cell Type	Procedure	Patient Group	Number	Operative Mortality	Survival
Epidermoid	Lobectomy	TL(a)	141	7 ± 2	36 ± 5
		PI(b)	52	8 ± 4	23 ± 6
		SO(c)	89	7 ± 3	46 ± 6
Pneumonectomy		TL	75	11 ± 4	19 ± 5
		PI	40	15 ± 6	17 ± 7
		SO	35	6 ± 4	21 ± 8
Adenocarcinoma	Lobectomy	TL	56	4 ± 3	26 ± 10
		PI(d)	7	14 ± 13	29 ± 17
		SO	49	2 ± 2	23 ± 12

(a) Total.
(b) Prior irradiation.
(c) Surgery only.
(d) Too few to be reliable.

*Mortality and survival as percent ± standard error.

my. Much of this difference may be attributed to selection of patients, since lobectomy and sleeve lobectomy in particular were performed on patients who might otherwise require a pneumonectomy. The collaborative study finds no effect of irradiation when patients are completely randomized.

With the exception of oat cell, histology did not appreciably influence survival in this series, and the collaborative study confirms this. Oat cell carcinoma did poorly in this series, as in others, because of early metastasis. There is one nine-year survivor of this cell type in this series, and other authors[5] have reported a seven-year survivor of oat cell treated with irradiation and nitrogen mustard.

The patients in this series were not staged by the TNM system as this has been only recently developed by Mountain.[6] Some inferences as to stage can be drawn, however. Lobectomy would likely be the procedure of choice for stage I, although pneumonectomy might also be done, especially if the ipsilateral hilar nodes were involved. Survival for this stage has been reported on the order of 35 percent at five years, and the survival for the patients receiving lobectomy in this series was 33 percent at five years, and 30 percent for lobectomy patients in the collaborative study. Stage II would probably require a pneumonectomy, five-year survival for which was 14 percent in this series and 20 percent in the collaborative study. Mountain reports five-year survival for stage II on the order of 12 percent. Treatment for stage III would be largely palliative. Most of the patients in this series were treated for cure, so no comparison is possible for operation and stage III. If all patients in this series who received a lobectomy or a segmentectomy were of stage I, then 63 percent of this patient population would be of this stage. This is

more than twice the percentage of stage I patients reported by Mountain, and more than twice the percentage of lobectomy procedures (29 percent) reported by the collaborative study. Similarly with stage II; if all pneumonectomy patients in this series can be considered to be of this stage, 28 percent would be of stage II compared to 5 percent reported by Mountain. The collaborative study reports 44 percent pneumonectomy procedures.

Other comparisons to be made between this series and the collaborative study are resection rate and overall five-year survival. Both were substantially higher in this series. Resection rate was 91 percent as opposed to 73 percent in the collaborative study, and overall five-year survival for this series was 26 percent compared to the order of 15 percent for the collaborative study and Mountain's series. These comparisons, extent of surgery performed, resection rate, and overall five-year survival rate suggest that this series contained more early disease than is generally reported in large, collaborative series.

The results of the different operations in this series suggest that segmentectomy is adequate curative surgery for localized disease. Those patients for whom a segmentectomy was deemed appropriate survived as long as those who received a lobectomy. This reinforces the trend toward more conservative surgery for this malignancy.

CONCLUSIONS

There is no evidence for a beneficial effect of routine preoperative irradiation for patients with bronchogenic carcinoma. This is not to say that irradiation is not worthwhile in converting a marginally operable patient into a suitable candidate for resection, since the patients in this series who were judged not resectable at thoracotomy were all dead within three years.

There is evidence that conservative surgery is indicated (segmentectomy *vs.* lobectomy) when the conservative approach will remove the entire tumor with an adequate margin. The patients do as well with segmentectomy and more respiratory capacity is preserved.

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REVIEW: IMMUNIZATION OF HUMAN AND SUB-HUMAN PRIMATES AGAINST PLASMODIAL INFECTION

Gary L. Simpson

INTRODUCTION

The malarial vector (the mosquito — genus *Anopheles*) had almost assuredly developed an integral partnership with the protozoan parasite (genus *Plasmodium*) long before any form approaching *Homo sapiens* appeared on the earth. It is also rather safe to assume that prehistoric man, at least in the warmer climates, suffered from periodic chills and fevers. Mention of a "malaria-like" disease is a constant feature of the earliest recorded chronicles, including lengthy descriptions in Chinese, Babylo-Assyrian, Indian, and Egyptian literature. In the millenia following these ancient accounts, (Table I), malaria has challenged some of the world's foremost medical researchers, while claiming millions of lives. With the eventual delineation of the plasmodial life cycle, the development of the residual insecticides (principally D.D.T.), and the institution of chloroquine (and other synthetic antimalarial) chemotherapy, "man's mastery over malaria" seemed imminent by the mid-1950's. The initiation by that time of a global eradication program by the World Health Organization (WHO) had promised to eliminate the disease within a generation. It is now apparent that those predictions were premature.

In addition to the tremendous financial burden that eradication efforts have placed on the meager resources of some of the poorer nations, and the uncertainty of their co-operation over extended periods of time, the documentation of the emergence of parasite drug resistance[1] and vector insecticide resistance[2] have forced a re-evaluation of the problem. This is not to imply that WHO initiatives in malarial control have not been successful. A 1972 WHO report[3] estimated that 1.346 billion, of the 1.826 billion population which lives in areas originally at risk to malaria, are under some measure of protection. However, certain observations (including those cited above) have begun to question the continued maintenance, extension, and efficacy of these programs. For instance, although current prevalence and mortality statistics of malarial disease are extremely difficult to obtain, a recent WHO Technical Report[4] estimated that in 1971 there were nearly seven million registered cases of malaria in a portion of the WHO African region, representing a base population of approximately 166 million persons. Mortality figures of deaths directly attributable to malaria ran as high as 1.27 percent. It can be assumed that both estimates represent lower limits of actual figures owing to the common under-reporting of cases in endemic areas. In addition, it is presently conjectured that a great potential threat may lie in the reintroduction of the vector into communities where immune levels have dropped during its temporary absence. This possibility has been tragically documented by Bruce-Chwatt in a study of the 1967 outbreak in Ceylon, in which over a million cases of malaria were reported.[5]

As a result of these findings, a renewed interest in the improvement of anti-malarial chemotherapy and in the feasibility of malaria vaccination has been noted. This discussion will review the progress made to date toward the development of a malaria vaccine applicable to primate systems.

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TABLE I

HIGHLIGHTS OF ADVANCES MADE IN THE UNDERSTANDING OF MALARIA

IN APPROXIMATELY 350 B.C.: Hippocrates described the malarial fevers (quotidian, tertian, and quartan).

IN THE EARLY 1600's: A Jesuit missionary in Peru was cured of malaria with the bark of the "fever tree" (Cinchona), leading to the discovery of quinine. Quinine became the drug of choice for all types of malarial infection until the 1940's.

1716: Lancisi described a pigment (later to be called hemozoin) in tissues of individuals infected with malaria.

1880: Laveran, a physician in the French army and professor at the Val-de-Grâce, identified the plasmodial organism while examining a smear of fresh blood. (He received the Nobel prize in 1907 for his discovery).

1884: Marchiafava and his co-workers delineated the asexual cycle of the parasite in human erythrocytes.

1885: Golgi showed that the fever paroxysms of malaria coincided with the phase of erythrocyte rupture by merozoites (and subsequent reinfection of other red blood cells).

1897: MacCallum (a medical student at Johns Hopkins) discovered the process of fertilization that explained the sexual and asexual types of parasites in the blood.

1898: Ross, and Bastianelli and co-workers, independently, demonstrated that malaria was transmitted by mosquitoes. (Ross received the Nobel Prize in 1902 for the discovery).

WORLD WAR II ERA: (1) D.D.T. and other residual insecticides were initially utilized for vector control. (2) Chloroquine and other synthetic anti-malarials became the treatment of choice for malaria.

1948: Shortt and his colleagues discovered the exoerythrocytic maturation phase in the liver, which provided an explanation for the relapsing nature of the malarial infection.

1960-1964: Emergence of resistance of *falciparum* malaria to chloroquine and other synthetic anti-malarial drugs in South America and Southeast Asia.

PLASMODIUM: LIFE CYCLE, INFECTION AND IMMUNITY

To serve as a basis for orientation, summaries of the life cycle of malaria parasites, of the major pathological effects of the infection, and principal aspects of derived immunity may be reviewed. A general discussion of these processes can be found in I. N. Brown's "Immunological Aspects of Malaria Infection."[6] A detailed consideration of plasmodial life cycles, particularly taxonomy and morphology, can be found in "Malaria Parasites and other Haemosporidia," by Garnham.[7] Recent articles by Conrad[8] and Maegraith and Fletcher[9] offer an excellent understanding of the known pathophysiological effects of the infection. Finally, Cohen and Butcher[10] have published the latest review of aspects of the immunological response to *Plasmodium*, and have emphasized the lack of precise information in this area.

To briefly summarize, malaria is the result of a protozoan infection transmitted by the bite of the *Anopheles* mosquito, and characterized by paroxysms of fever, symptoms of a hemolytic anemia, chronicity (with relapses), and variable severity. The immunity from naturally acquired infection is not sterilizing, nor is it protective against infection with other strains or species. Plasmacytoid response seems to be the predominant mode of immunological defense, with as yet no primary role demonstrated for cell-mediated processes.

From study of the referenced articles, the difficulties of perfecting a malarial vaccine become apparent. The complexity of life forms, antigenic variation, premunition, and strain and species specificity are some of the bothersome problems which must be overcome before a practical and effective vaccine can become a reality.

HUMAN VACCINATION EXPERIMENTS

The first report to describe attempts at immunizing humans against malarial infection appeared in 1930. In those studies, Konstansoff prepared autovaccines by denaturing parasites with 0.2 to 0.3 percent phenol, after erythrocytic lysis with distilled water. The injection of these "killed" parasites was claimed to have elicited a gradual acquisition of immunity.[11] Similarly, in 1946, Boyd and Ketchen[12] published the results of clinical trials of autovaccination against *Plasmodium vivax,* but varied the denaturation of the plasmodial agents *in vivo.* Parasitized cells of infected patients were introduced (I.V.) into non-immune subjects with high serum levels of quinacrine. The non-immune individuals were able to clear rapidly the parasites from their circulation. The end result was a partial immunity against subsequent challenge with an homologous strain of *P. vivax,* specifically a less severe infection than one would predict in a fully susceptible person.

Beginning in 1946, Heidelberger and his colleagues (from Columbia University and the University of Chicago) published the results of an extensive series of human immunization attempts. These attempts, conducted during World War II (1942-1945), represent a level of human experimentation which has not been approached for sheer number of patient participants. In the major effort of the series, a total of 179 patients suffering from relapsing *Plasmodium vivax* malaria were divided into the following groups:

Group 1 — 58 patients received the standard chemotherapy of the time (the standard group of comparison).

Group 2 — 59 patients received injections of formalin-treated *P. vivax* parasites (the experimental group).[13]

Group 3 — 62 patients received injections of formalin-treated normal human erythrocyte stromata (the control group).

Rates of relapse amongst the three groups were constant. No effect of the immunization or of drug therapy was noted in preventing relapse.[14] In subsequent experiments, non-infected subjects were given an inoculum of 3.5×10^9 to 10×10^9 formolized *P. vivax* parasites — seven to nine injections by intracutaneous, subcutaneous, and intravenous routes. Challenge (in one experiment with trophozoite-stage parasites and in one with sporozoite-stage parasites) followed the final injection of the immunization schedule by three weeks. In both instances, all subjects developed an infection of normal virulence and duration.[15,16]

A number of thoughts have emerged to account for these failures. Heidelberger himself felt that a soluble, but essential, antigen had been lost during preparation of the injection samples. Others have blamed the lack of a practical adjuvant as the major factor. The most that can be said of the attempts by Heidelberger and his colleagues is that they represented the first methodical approach to human experimentation with malarial vaccines. At present, they also represent the last large-scale attempt at the artificial induction of immunity in humans.

Recently two isolated reports of human immunization trials with sporozoites have appeared. The trial reported by Clyde, et al.[17] in 1973 involved three subjects. Mosquitoes infected with *Plasmodium falciparum* were X-irradiated (thus inactivating the sporozoites *in vivo*[18]), and allowed to feed on the volunteers over an 84 day period. On day 98, infectious challenge was accomplished by exposing the subjects to non-irradiated mosquitoes infected with the homologous *P. falciparum* strain. One of the three volunteers demonstrated a measure of protection to the sporozoite challenge, but remained susceptible to strain-specific falciparum malaria induced by direct blood transfer. Rieckmann, et al.,[19] using a similar technique, have reported successful immunization of one volunteer.

SUB-HUMAN PRIMATE VACCINATION EXPERIMENTS

Consistent somewhat with the reports of the Heidelberger group, early sub-human primate trials without the use of adjuvants were unsuccessful,[20,21] although investigators involved with these studies claimed to have induced malarial antibody.[20,22] The introduction by Freund in 1944 of an adjuvant containing a "lanolin-like substance, paraffin oil, and killed tubercle bacilli"[23] was to dramatically alter this situation.

Freund's complete adjuvant, together with subcutaneous injection of two doses of formolized *Plasmodium knowlesi*—parasitized blood (optimum: approximately 15×10^9 schizonts), effected a high degree of resistance to a normally lethal challenge.[24,25] Protected animals rapidly cleared their parasitemias if, indeed, any became apparent, and no subsequent relapse was observed. This represented the first successful vaccination attempt in primates, and interestingly, remained the only published data concerning the immunization of primates for nearly twenty years.

In 1965, a study, by Targett and Fulton, of injection routes found that conferral of immunity was greater when the research design included intramuscular, rather than subcutaneous, injection. The inoculum in both cases was a formolized parasite suspension emulsified in Freund's complete adjuvant. As before, antigen material without adjuvant did not protect. Controls consisting of adjuvant alone and normal host erythrocytes in adjuvant were also ineffective.[26]

The experimental protocol followed by Freund, et al.,[25] and Targett and Fulton[26] was revived and refined by K. N. Brown and co-workers in a series of reports beginning in 1968.[27-29] Immunizations with complete and incomplete Freund's adjuvant were compared, and the factors of premunition and humoral response were included in a carefully controlled study. Essentially, the results demonstrated a clear distinction between the degree and characteristics of the protective response seen following inoculation with the two Freund's adjuvants (used to emulsify *P. knowlesi* schizont-infected red cells). The "incomplete" group showed an immune response termed "variant specific," and all monkeys ultimately died. It was theorized that antigenic variation had allowed the parasite to overcome the immunity acquired through immunization. On the other hand, a more solid immunity was seen in the "complete" group. Most of the monkeys resisted any breakthrough by an antigenic variant. In both instances parasite agglutinins were detected; but only in the "complete" group did sub-inoculation not cause infections in susceptible hosts, and only in this group did splenectomy not result in a recrudescence of the infection.

Voller's group, in 1968, initiated a series of experiments in an attempt to translate the studies of the *P. knowlesi*-Rhesus monkey system into a system which would be more directly relevant as a human model: namely, the *P. falciparum*-Aotus monkey system. Vaccinating with formolized, schizont-infected erythrocytes, emulsified in Freund's complete adjuvant, Voller and his colleagues were able to show a slightly prolonged pre-patent period with immunized animals as compared to controls. However, once parasitemia was detected, the infection developed at the same rate as controls and ended in death for all vaccinated animals.[30]

In recent years, a different immunization approach has been pursued by several researchers.[31-33] Based on the original findings of Bennison and Coatney,[18] X-irradiation has been utilized in an attempt to provide inactivated-sporozoite immunizing material. Various primate systems, antigen preparation methods, injection routes and injection schedules, and challenge schemes have been used, but to date, no significant protection has been demonstrated. More encouraging results, however, have been obtained by Sadun et al.,[34] working with trophozoite antigens. Utilizing the *P. falciparum*-Aotus monkey system, infected erythrocytes were irradiated and four injections administered intravenously (in dosages ranging from $5 \times$

10^8 to 9×10^9 parasitized erythrocytes). Four of nine animals receiving the regimen survived infectious challenge, which followed one week after the final immunizing dose. Although the work is of interest, the data represented no improvement over the results of previously cited authors, who employed formalin as an inactivating agent.

In the early 1970's, Silverman and associates reported the successful vaccination of Rhesus monkeys against *P. knowlesi* challenge, utilizing a "partially purified" fraction derived from the trophozoite stage of the plasmodial parasite.[35] For the first time, material other than *whole* parasites had been used to induce artificial immunity in primates. The immunizing material was prepared from parasitized erythrocytes by differential French pressure cell disintegration and centrifugation, and molecular sieve chromatographic separation. The resulting preparation was emulsified in Freund's adjuvant and administered via a lengthy immunization schedule, involving multiple injection routes.

Following this initial success, a systematic, developmental approach was begun to establish a bio-assay vaccination model, using the *P. knowlesi*-Rhesus monkey system.* The adherence to the bio-assay concept required rigorous attention to the standardization of experimental parameters (e.g.: antigen preparation, vaccination procedures, immunization schedules, and monitoring techniques) and allowed the specific testing of multiple vaccination variables (e.g.: altered immunization and challenge schedules, varied modes of infectious challenge, efficacy of antigen fractionation products, assessment of alternative adjuvants, etc.). In 1973, Schenkel, Simpson, and Silverman published the first of a series of papers describing the details of this malarial vaccination model (see outline in Fig. 1), and their initial attempts at manipulating its parameters.[36,39,40] Each progressive study has re-affirmed the antigenic efficacy (see Fig. 2) of the void volume eluate preparation (described in Fig. 1), and has extended understanding of the system.

The first experimental trials involved efforts to find an alternative to Freund's adjuvant (which tended to cause sterile abscesses in test animals). Monkeys receiving antigen material emulsified in sodium alginate. BCG, and Poly A:U (a synthetic polymer) plus aluminum hydroxide, were compared to non-injected controls and baseline controls (i.e., animals receiving antigen emulsified in Freund's adjuvant).[35,39] Although none of the non-Freund adjuvant mixtures proved effective, subsequent data[41] suggested that a different preparation of aluminum hydroxide (an adjuvant acceptable for human use) might be adequate when used alone with the void volume eluate antigen material.

A report by the authors in 1974[40] focused on the further fractionation of the void volume eluate material by linear sucrose density gradient centrifugation (see Fig. 3), and the testing of the fractionation products (Peaks I and II) in the bio-assay system.[42] The monitored responses (summarized in Table II) could be generally categorized into three classes: 6/9 vaccinated animals Groups 1, 2 and 3) which demonstrated parasitemias of 0-7.5 percent and survived; 3/9 vaccinated animals (Groups 1, 2 and 3) which demonstrated similar parasitemias, but did not survive; and 4/4 control animals (Groups 4 and 5) which demonstrated extremely high parasitemias of up to 60 percent and died. Once again, a significant decrease in parasitemia and an increase in survival (following *P. knowlesi* challenge)

*As an aside, it should be stressed that the *P. knowlesi*-Rhesus monkey system represents a very useful system for vaccination studies. *P. knowlesi*, when introduced into the Rhesus host, produces a consistently lethal infection which results in parasitemias approaching 90 percent and death of the animal within five to ten days. It also should be noted that the Rhesus monkey is not considered a natural host of *P. knowlesi* and, therefore, the probability that any experimental animal has had previous immunological experience with the parasite is extremely remote.

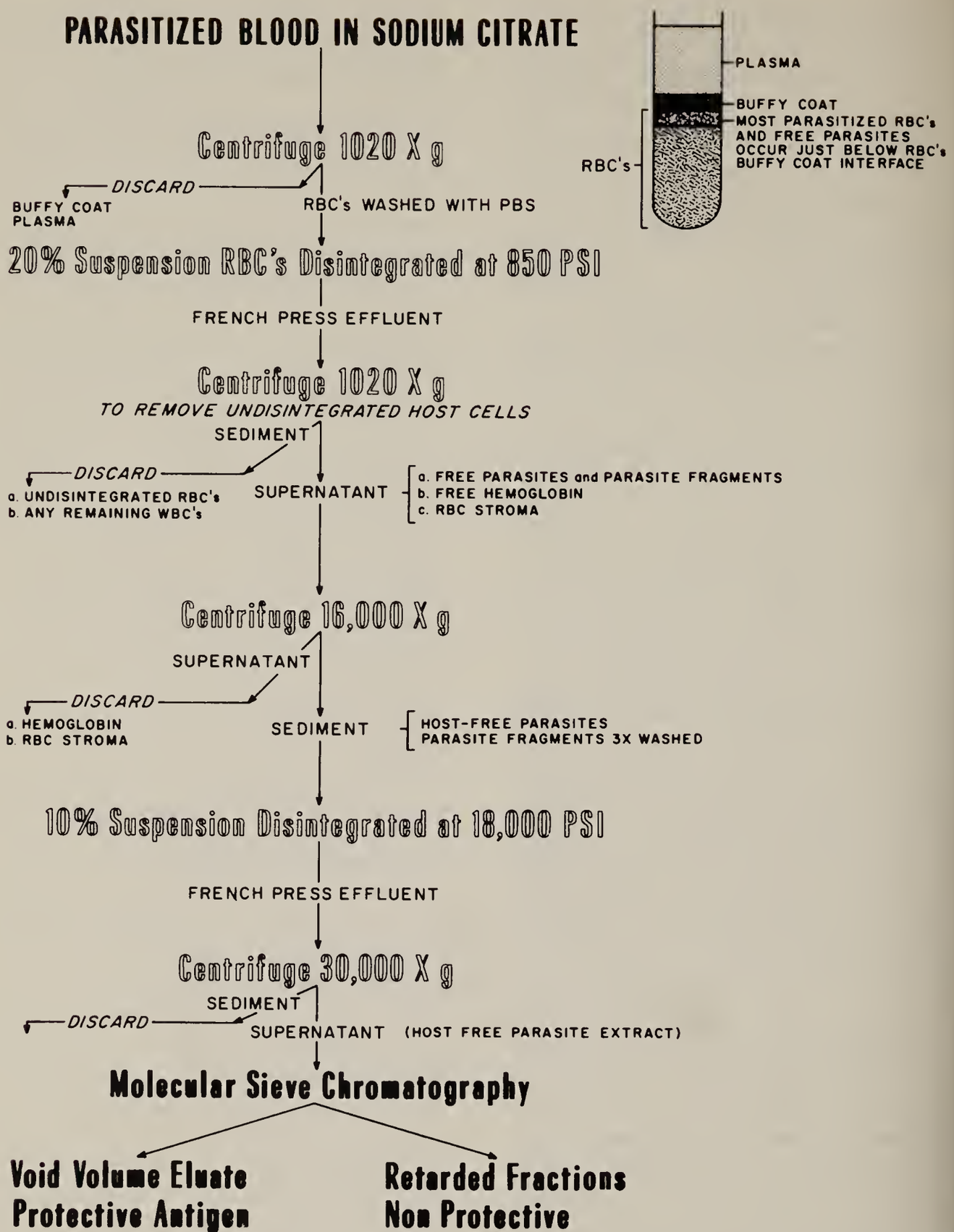

Fig. 1—Antigen preparation followed the protocal detailed by Schenkel, Simpson, and Silverman.[36,39] After primary centrifugation of parasitized whole blood (heparinized) to enable the buffy coat of leukocytes to be removed, a 20 percent erythrocyte suspension was passed through a French pressure cell (FPC: American Instrument Co., Inc., Silver Springs, Md.) at a pressure of 850 psi (5.86×10^6 N/m^2 I.U.). The procedure served to destruct preferentially host erythrocytes yielding a parasite slurry which after the prescribed washings, was seemingly free of significant contaminating, erythrocytic stromata (Killby and Silverman[37]; D'Antonio, von Doenhoff, and Fife[38]). Disintegration of the parasites was accomplished by a second FPC passage at 18,000 psi (1.24×10^8 N/m^2 I.U.). The supernatant was subjected to molecular sieve chromatography (see Fig. 3) and the resulting void volume eluate utilized as the immunizing material.

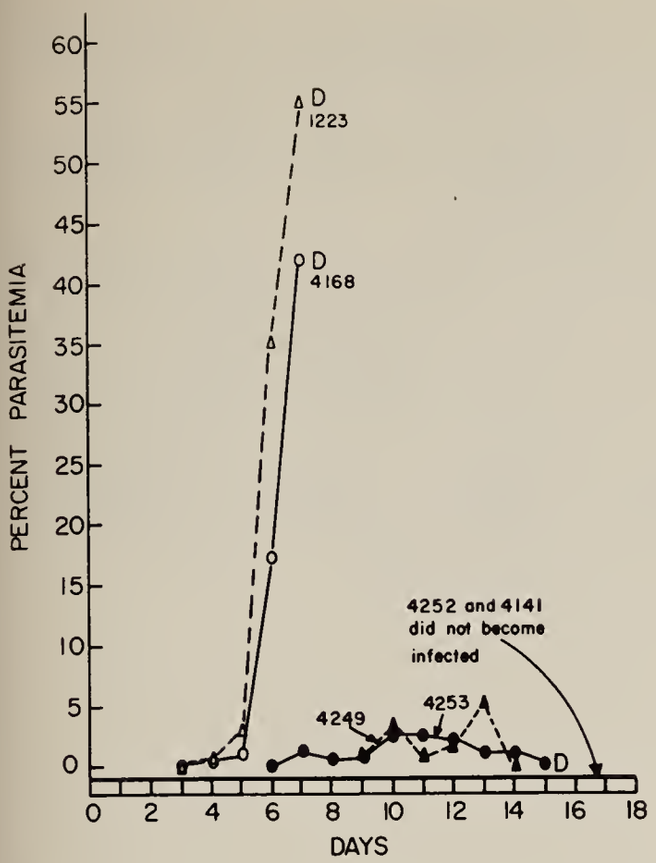

Fig. 2—The graph depicts typical responses of vaccinated and control animals in the *P. knowlesi*-Rhesus monkey system. The profiles of animals 1223 and 4168 are representative of the fulminant course of the malarial infection in unprotected monkeys. Animals 4141, 4249, 4252, and 4253 demonstrate the striking contrast of the response of vaccinated animals to infectious challenge.

was induced in Rhesus monkeys by the administration of non-viable plasmodial antigen fractions.

One of the more striking observations resulting from the above experiments (and one which had been made by most investigators employing the *P. knowlesi*-Rhesus monkey system) concerned the drop in red blood cell profiles following challenge. After a slight initial rise in both RBC counts and microhematocrits, these blood indices dropped dramatically. This was noted even in protected groups where parasitemias remained either less than 5 percent or remained entirely undetected (see Fig. 4). The etiology of the anemia could be postulated as due to the natural course of the infection, to some complication of the vaccination process, or to both.

Erythrocyte destruction greater than that predicted from the percentage of cells infected, is well documented (see Zuckerman's review).[43] Proposed explanations have included: a) enhanced phagocytosis of non-infected cells,[43-46] b) postulated immune mechanisms such as opsonizing, or (Type II or III) auto-immune lytic processes,[47-49] and c) splenic pitting (i.e., mechanical removal of parasites in sinusoidal walls with return to the circulation of short-lived, damaged spherocytes.[8,50] In addition, certain factors of the experimental design may have been relevant. Unlike in previous trials, juvenile (1.5 kg weight) Rhesus monkeys, rather than adult animals (6 to 7 kg) were utilized to simulate the immune status of children. Moreover, the challenge inoculum was extremely large, 2×10^7 parasitized erythrocytes for the initial challenge.* The extent of contributions of each of these parameters or combination of parameters to the observed hemolysis, is unknown.

In spite of the significant advances in active immunization of primates, numerous problems persist. Some research is currently centered in the following areas:

*Analysis of minimum infective dosage in the *P. knowlesi*-Rhesus monkey system by Schmidt[51] has demonstrated that the number of parasitized erythrocytes sufficient to cause death approaches five.

1) purification and characterization of the specific immunogenic components of trophozoite antigen preparations.
2) evaluation of sporozoite-phase infectious challenge of animals immunized with trophozoite antigens.
3) development of an immunoassay which would allow quantification of specific immunological responses to immunizing antigens.
4) translation of the principles of the *P. knowlesi*-Rhesus monkey system into a system more relevant to human application (e.g., the *P. falciparum*-Aotus monkey system).
5) continued evaluation of adjuvants which would be acceptable for human use.
6) consideration of the potential need for a polyvalent malarial vaccine (i.e., a vaccine composed of both trophozoite and sporozoite antigens).
7) persistent efforts to develop *in vitro* cultivation techniques to allow massive production of plasmodial antigen material.

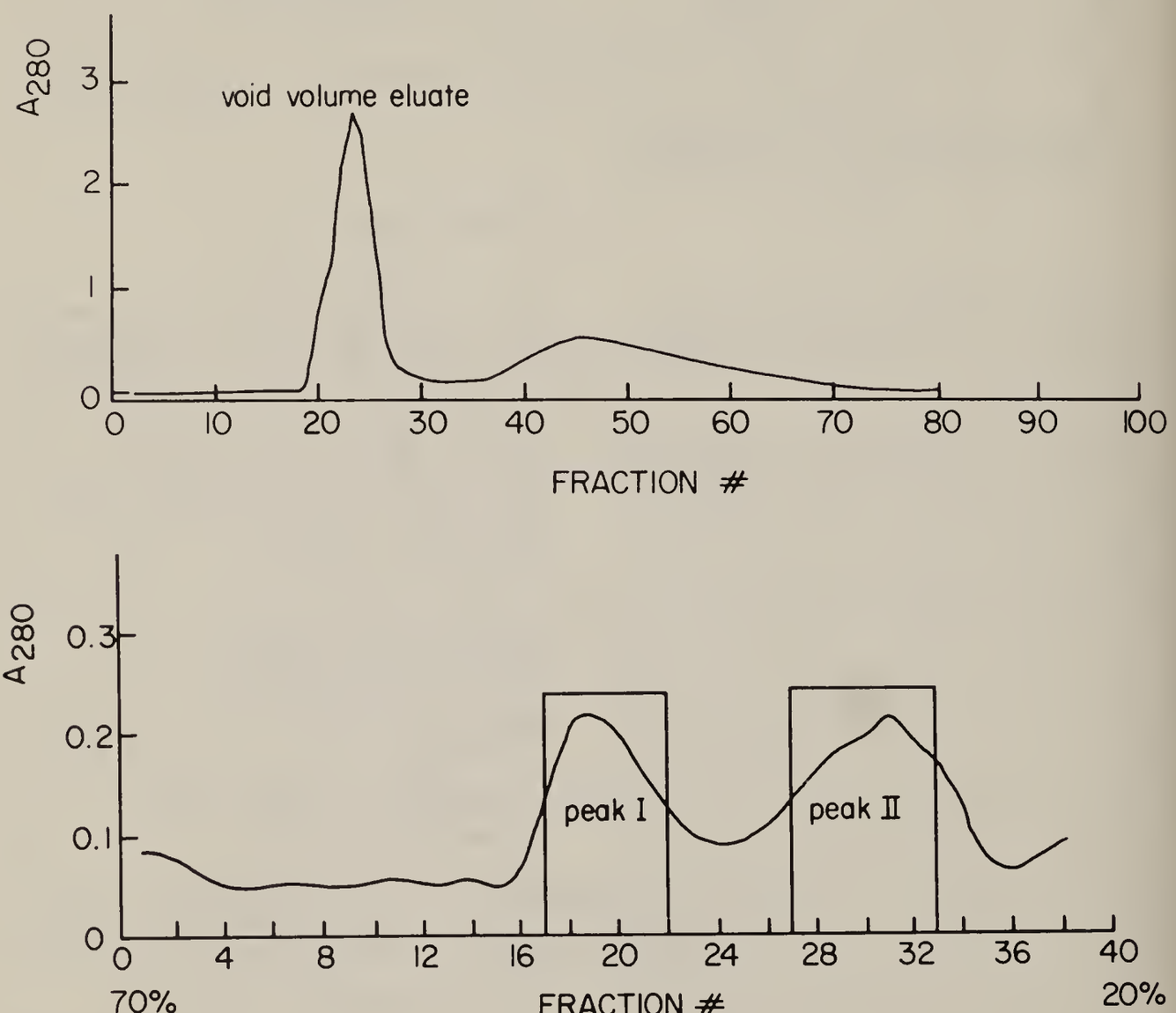

Fig. 3a & b—After initial preparation via the protocol outlined in Fig. 1, fractionation of the void volume eluate (resulting from molecular sieve column chromatography—see 3a) was accomplished by linear sucrose density gradient centrifugation.[42] The gradients, with teminal concentrations of 20-70 percent, were prepared by means of a gravity flow apparatus at 4°C. Each cellulose tube contained a total of 29.0 ml. Centrifugation (at 25,000 r.p.m. for 240 min. at 4°C.) was carried out in the Beckman Model L ultracentrifuge, equipped with a SW 25.1 head (Beckman, Spinco Division, Palo Alto, California). Samples (0.7 ml) were collected by means of a fractionator using needle puncture of the gradient tubes. A typical profile is seen in Figure 3b. Vaccination preparations consisted of respectively pooled peaks 1 and 2. Sample pools were dialyzed overnight against phosphate buffer saline (two to three changes) to remove the sucrose.

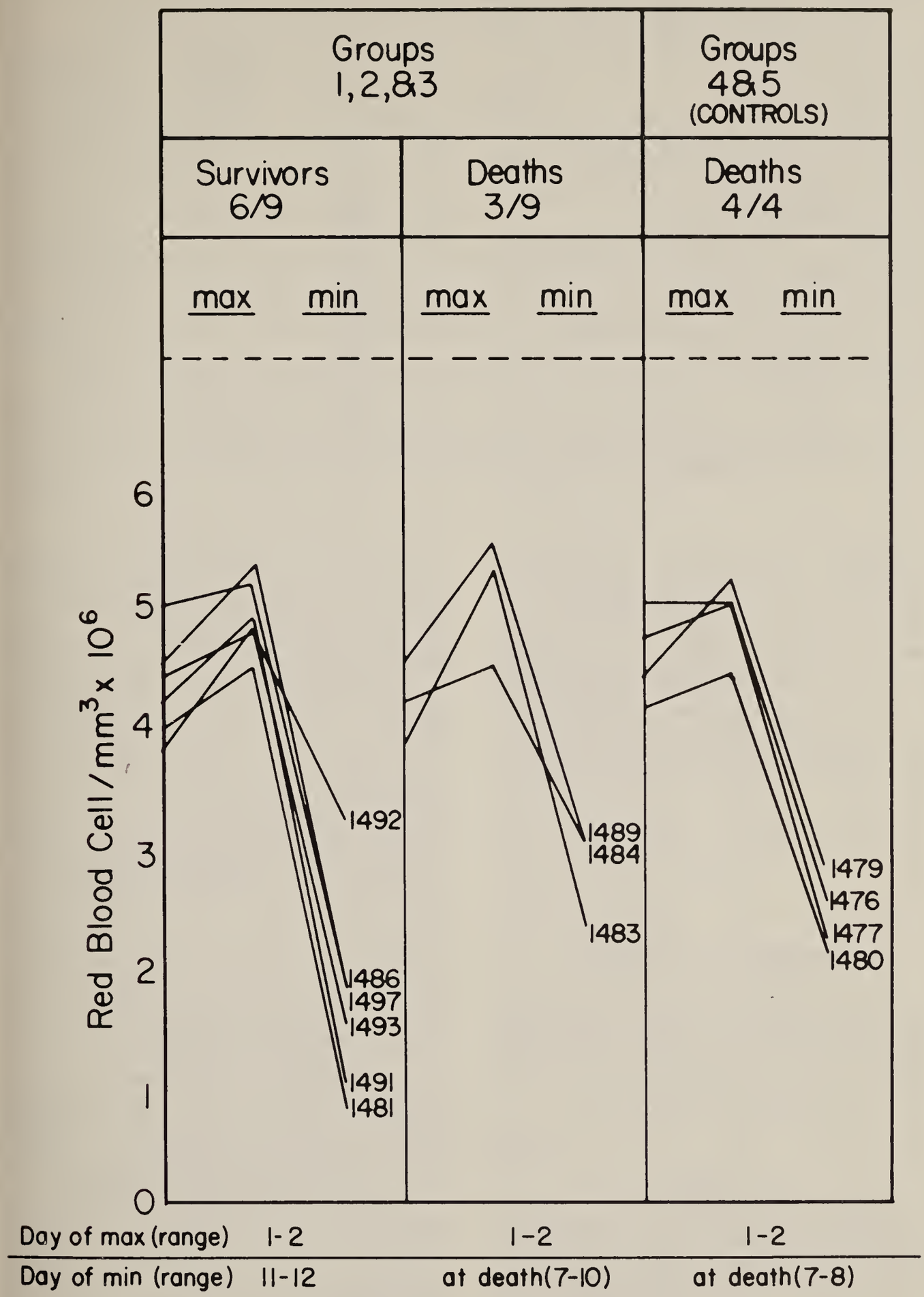

Fig. 4—Scattergram depicting the minimum and maximum RBC counts monitored following challenge. Animals are divided into the three defined classes (vaccinated—surviving; vaccinated—fatality; control).

TABLE II

TREATMENT, SURVIVAL, AND PEAK PARASITEMIAS OF VACCINATED AND CONTROL MONKEYS CHALLENGED WITH NORMALLY LETHAL *PLASMODIUM KNOWLESI*

Treatment	Group No.	Monkey No.	Monkey surviving challenge = +	Peak parasitemia after initial challenge
Bio-Gel void volume eluate preparation in Freund's adjuvant	1	1486	+	< 0.5
		1481	+	7.5
		1493	+	2.5
Peak 1 sucrose density gradient fraction in Freund's adjuvant	2	1484	–	0.0
		1489	–	0.5
		1491	+	2.5
Peak 2 sucrose density gradient fraction in Freund's adjuvant	3	1483	–	6.0
		1492	+	< 0.5
		1497	+	< 0.5
Bio-Gel void volume eluate—no adjuvant*	4	1476	–	50.0
		1477	–	58.0
Freund's adjuvant—no antigen	5	1479	–	24.0
		1480	–	48.0

*In earlier published data[39] the void volume eluate without adjuvant had been shown to be non-protective, thus, this group constituted an additional control.

One will note that many of the remaining obstacles seem to require technological progress rather than the establishment of major, new, biological concepts. It also would seem that the work summarized in this review continues to raise the hope that vaccination of humans may be a feasible adjunct to global malarial eradication programs.

ACKNOWLEDGEMENT

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Anesthesiology

Schmidt GB, Meier MA, Sadove MS: Sudden appearance of cardiac arrhythmias after dexamethasone. *JAMA 22:1400. 1972*

A 43-year-old woman was given 100 mg of dexamethasone intravenously the evening after aortic and mitral valve replacement. Immediately thereafter she developed very frequent multifocal premature ventricular contractions which subsided with the intravenous administration of lidocaine (Xylocaine 2 percent). Later she was given 50 mg of dexamethasone intravenously, and the arrhythmias recurred. The pathogenesis of these severe arrhythmias in this already stressed myocardium is uncertain. There is a possibility that it might be due to the preservatives.

Cardiovascular Surgery

de Takats G: Sympathectomy for hypertension. *Am J Surg 127:521, 1974*

Sympathectomies are not performed today for essential hypersion, although in the 40's, this operation was very much in vogue. A revival of interest in a modified and restricted form, denervating only the target organs of kidney and adrenal is suggested. It is indicated in patients whose hypertension is refractory to medical management and in patients who are unable or unwilling to stay on a permanent hypertensive medication. Except for terminal renal impairment, it is an easy choice before bilateral nephrectomy followed by life-long dialysis or renal transplantation is contemplated.

de Takats G: The urokinase pulmonary embolism trial. *Editorial, Am J Surg 126: 311, 1973*

This editorial points out the difficulties of carrying out a large multi-institutional trial evaluating the thrombolytic activity of urokinase in pulmonary embolism. In contrast to the excellent statistical design of the project, the management of the individual patient admitted to the study could not be optimal. The fluctuating requirement for anticoagulant and fibrinolytic drugs could not be met by inflexible protocol. While this painstaking cooperative venture showed that urokinase lysed the clot faster in the first 24 hours than heparin, later morbidity and mortality did not differ. Bleeding occurred frequently in both groups and urokinase is unavailable at present.

Najafi H: Pulmonary artery aneurysm associated with mitral valve disease; a grave prognostic sign. *Chest 62:669, 1972*

Seven patients with advanced mitral valve disease and systemic pulmonary hypertension subjected to mitral valve replacement without survival are presented here with the common denominator or the characteristic additional finding of aneurysmal dilatation of the

pulmonary artery. During the same period 16 other patients with similar degree of valvular dysfunction and systemic pulmonary hypertension underwent mitral valve replacement, with nearly 50 percent of them surviving the operation. The only major difference between the two groups was the presence of pulmonary artery aneurysm in the former group with uniformly fatal termination. It is suggested that this roentgenographic sign "under the circumstances outlined" indicates extremely grave prognosis for mitral valve replacement, and, therefore, consideration should be given to either no operative treatment or closed mitral commissurotomy if at all feasible.

Bronchoesophagology

Holinger PH, Brubaker JD: Still and motion picture photography of the tracheobronchial tree and esophagus through endoscopic telescopes. *Ann Otol Rhinol Laryngol 81:809, 1972*

The Hopkins and rod-lens telescopes made by Karl Storz Endoscopy-America, Inc., Germany, have provided superior light transmission efficiency and superb image resolution. They are used for both stills and movies to document the endoscopic pathology of the larynx, tracheobronchial tree and esophagus of adults, children and infants. Technical details of the light sources, films, cameras, lenses and exposure factors are given. Representative endobronchial photographs in black and white are shown, although all original photographs are in color.

Holinger PH, Zimmerman AA, Schild JA: Tracheobronchial tree malformations. *In: Pediatric Otolaryngology, Vol. II, Ed by Charles F. Ferguson and Edwin L. Kendig, Jr., 1972, Philadelphia, W. B. Saunders Company*

This chapter is a contribution to a superb, thorough, and complete two-volume textbook of pediatric otolaryngology and its related subspecialties. The chapter classifies congenital anomalies encountered clinically and correlates them with the embryology of the tracheobronchial tree and development of the total form of the lungs. It is noted that the definite pattern of lung formation is completed early in the third month of intrauterine development (3 cm. fetus), as illustrated by photomicrographs. During this early differentiation the primordium is most vulnerable to noxious influences such as viral toxins and oxygen deficiencies. Any interferences with the chemical constituents of cells may severely affect mitotic activity during this critical stage. Constrictions, enlargements, evaginations, abnormal bifurcations and other anomalies of gross morphology of the trachea and bronchi are discussed. Anomalous bronchial and lung tissues attached to tissues other than the respiratory system (sequestrated lungs), supranumerary bronchi and lobes and the effects of anomalies of the cardiovascular system on the developing tracheobronchial tree are illustrated by bronchograms and esophagrams.

Community Medicine

Christman L: the critical issues of community mental health. *In: Controversies in Community Mental Health, H. Gottsfeld, Editor, 1972, New York, Behavioral Publications, pp. 5-21*

In this chapter an attempt is made to compare the structure of hospital care for emotionally disturbed persons with that of community mental health facilities. Management of

maladaptive behavior, for most persons, seems to have most success if it can be done in the ordinary environment of the disturbed person rather than in the artificial atmosphere of hospitaliation. Professional persons working in the community day-to-day are likely to be more aware of the fine shades of differences in the problems that are troublesome. One is better able to rank these problems, choose which to attack first, and deal directly with dissonant factors when one is in a position to perform sophisticated intervention. Patient care or client assistance can be conceptualized in a unitary form that is process-oriented and empirically bound to the community.

The dissemination of knowledge about emotional health into a community is better accomplished when linked to actual practice, a linkage system made visible in the very structure of the professional services of the community staff. In addition, community-based service makes it easier to develop programs geared to reduce the incidence of illness. There probably is no single outstanding model for effective community-based services. There will be variations on the theme of interdependence between workers. Some general principles will be part of all. Shared interpretations of goals and means, a system where mutual expectations can be fulfilled through the process of complementation, facilitation of each other's roles, self-direction without anarchy, a sense of professional destiny and personal self-fulfillment are all attributes useful to the successful mobilization of interdisciplinary resources. Community-based mental health services, if effectively organized, have the potential for being of inestimable value in delivering help to troubled people.

Turner IR: Free health centers: A new concept? *Am J Public Health 62:1348, 1972*

The "free" clinic movement appeared nationally in the late sixties. Of 175 such clinics, approximately one-third were in California and the rest in 31 other states. A dozen Chicago clinics flourished between 1968 and 1972 and about six still function. Unlike those in California, their central focus was "free" care to poor and minority groups, less on students' health problems and drug abuse.

The Chicago clinics were organized and administered by a variety of groups, but were staffed by volunteer physicians, nurses, students, and community residents. Equipment and supplies were mostly donated. Paucity of funding and limited physician staff were the two major problems. A third was harassment by city health agencies.

The services provided varied from first aid to prevention and detection programs of a special nature.

Major principles espoused by the free clinics were 1) health care should be free at the point of delivery, 2) the communities served should have control of clinic functions, and 3) the present system is a failure and free clinics offer a model for new health care delivery.

The concept of "free" medical care is not exactly new. Many major medical institutions had their roots in "free" clinics. The Central Free Dispensary, progenitor of Rush Presbyterian-St. Luke's Medical Center was organized more than 100 years ago, with the objective:

> ". . . . . to aid persons who are sick and unable to pay for medical attention and to do this . . . efficiently and with no pecuniary profit. . . ."

The tragedy is that more than 100 years have elapsed, and poor and minority groups still seek adequate and humane health care by organizing free clinics, dependent upon volunteers and gifts.

There is far less controversy now over their existence than when they were first organized. Their supporters view them as a means for providing limited health services and as an opportunity to educate communities around health issues. Their detractors continue to view them as "store-front" medicine as a futile exercise which might otherwise be directed toward pressuring the health care system into providing more adequate and humane treatment to all who need it.

There is evidence to suggest that free clinics had some impact on health care in Chicago. The planning and operation of new health care facilities by the Board of Health is seen as attributable to the existence of the free clinics. Some presently functioning clinics are also negotiating to become outreach facilities of the major providers.

Whether free clinics are a new concept, they are one part of the continuum for change for restructuring health care systems.

Cytogenetics

Marczynska B, Pigon H: Karyological analysis of African cane rat *(Thryonomys swinderianus)*. *Cytologia 37:513, 1972*

Cytogenetic studies of African cane rat *(Thryonomys swinderianus)* established a diploid chromosome number for this species $2n = 44$. Among 21 pairs of autosomes, one pair of large submetacentric chromosomes possesses secondary constriction and satellites on the shorter arms. The X chromosomes are the largest metacentrics, while the Y chromosome is the smallest of the complement. The karyotypic similarities between African cane rat and other hystricomorph rodents are briefly discussed.

Hospital Administration

Christian JR: The governing board's responsibility for medical care. *The Hosp Med Staff 1:32, 1972*

The traditional approach to medical care and the failure of the medical profession to provide total health care have been challenged. Health care delivery systems are being subjected to critical scrutiny. The most conspicuous instrument for providing health resources, manpower, and services at the community level is the hospital. Accountability for all aspects of hospital operation, including guaranteed continuous quality in the delivery of health care, is the sole responsibility of the hospital's governing board. This responsibility involves a legal and moral obligation. The autonomy and self-determination of physicians, other health professionals, and owners and controllers of health care facilities have been challenged by the consumer, the community, and third-party payers. As a result, greater responsibility and accountability is required of the health care system and its providers. One of the most effective ways to delineate such responsibility and accountability is through the bylaws of a health care institution. The medical staff also must provide a set of bylaws through which its accountability to the governing board can be established. Adequate orientation of new members is essential to successful functioning of the board. The size and makeup of a governing board should reflect the size and complexity of its institution. Qualified consultants can advise board members on projects for which there is no board expert. The supreme challenge for the governing board of any institution is the removal of an ineffective member. The selection and appointment of a chief executive officer is the most crucial duty of the governing board. His degree of authority is established through guidelines set forth by the governing board. Medical staff appointments and reappointments and assignment or limitation of staff privileges are responsibilities of the governing body. However, recommendations for these decisions usually are made by the staff to the board. Through its bylaws, the medical staff establishes a framework of accountability to the governing board. Cooperation between the governing board and the medical staff can be encumbered by inadequate or unreasonable lines of communication. Physician participation in the meetings of governing board can aid in destroying the towers of suspicion.

Christian JR: The role of the physician as a member of the hospital governing board. *Ariz Med, Feb, 1972*

The assignment of specific functions of review, analysis and evaluation of medical care to the medical staff is erroneously interpreted as complete delegation of legal responsibility by the hospital governing board. The failure of some physicians to totally accept legal decisions which unequivocally obligate the hospital governing board with the ultimate legal responsibility for the quality of medical care, creates a dilemma. An obvious solution is the active participation of the physician as a member of the hospital governing board. Guaranteed quality is essential for success. This can only be accomplished through a coordinated effort of the medical staff and the governing board. The decrease of autonomy and the careful delineation of rights of self-determination are obligating the health care system and its providers to greater responsibility and accountability. It is the responsibility of the board to ensure protection to the corporate structure, the sponsoring group, the physician, the patient and the community, through the establishment of an adequate system of review. The medical staff, through its bylaws, establishes a framework of self-government and an accountability to the governing board. At the 1971 meeting of the AMA House of Delegates, the role of the medical staff member on the hospital governing board was considered. The criteria and methods for selection of nominees were established and suggestions regarding the role of physician members were presented. In this critical period of review, when professional and accreditation agencies are reversing their attitudes toward the physician's role on governing boards, the mechanism of the delivery of health care including planning, development, utilization, financing, quality control, consumer participation, manpower distribution, educational implications etc. becomes a challenge. This challenge must be accepted by the physician, immediately.

Infectious Disease

Cross A, Landau W, Levin S, Edwards LD: Resistant *Proteus rettgeri*. *Program and Abstr, 12th Intersci Conf on Antimicrol Agents and Chemother, pp. 90-91, Sept. 1972*

The presence of a non-motile, non-lactose fermenting *Proteus rettgeri* is reported. The organism, obtained primarily from urine cultures, was identified by growth on appropriate media and biochemical tests, and further delineated by its unique resistance pattern to antimicrobials. It was resistant to every major antimicrobial tested by the Kirby-Bauer method including gentamicin, nebramycin, kanamycin, tetracycline, chloramphenicol, carbenicillin, polymixin, ampicillin and cephalothin. Tube dilutions were performed by our laboratory and by the NCDC, Atlanta, Ga. The MIC was 500 ug/ml or greater with all these antimicrobials except gentamicin which had a MIC of 125 ug/ml. Rifampin was the only active agent *in vitro* with a MIC of 0.78 ug/ml at 24 hours; however luxurious growth ensued at 48 hours. Checkerboard analysis was done with the following combination: colistin and gantrisin, colistin and rifampin, gentamicin and rifampin and carbenicillin and rifampin. Colistin and rifampin were most effective *in vitro* at a level of 2.5 and 7.5 ug/ml respectively; rifampin alone and rifampin in combination with colistin however were totally ineffective *in vivo*. No R factor was demonstrable.

Cross A, Landau W, Levin S, Edwards LD: *Proteus rettgeri* outbreak on a medical floor. *Program and Abstr, 12th Intersci Conf on Antimicrob Agents and Chemother, pp. 90-91, Sept. 1972*

Over a three month period a *Proteus rettgeri* organism infected ten patients restricted to one general medical floor. This organism was resistant to all antimicrobials tested by the Kirby-Bauer and tube dilution methods including nebramycin, gentamicin, kanamycin, carbenicillin, ampicillin, cephalothin, tetracycline, chloramphenicol, polymixin and rifam-

pin. Clinical illness from the organism was directly related to local or systemic host deficiencies. Typically, patients were chronically ill with recent urinary tract instrumentation and infection and previous antimicrobial therapy. Two immunosuppressed patients became infected, one after renal transplantation. The latter had a renal abscess from which the organisms was cultured at autopsy. Although no antimicrobial was effective against the organisms, none of the four deaths that occurred was directly attributed to this infection. No reservoir was shown upon culturing personnel, the hospital environment and the stools and urine of every patient on the ward. Periods of hospitalization indicated the organism was spread by contact from patient to patient or through the intermediary of hospital personnel. Control was obtained by glove technique of personnel and contact isolation of patients. The importance of this organism is stressed by the fact that no therapeutic agent was effective *in vivo* or *in vitro*.

Levin S, Nelson KE, Spies HW, Lepper MH: Pneumococcal meningitis: the problem of the unseen cerebrospinal fluid leak. *Am J Med Sci 264:319, 1972*

A study was done of all patients treated for pneumococcal meningitis at the Municipal Contagious Disease Hospital, Chicago, Illinois, between 1954 and 1968, to estimate the frequency and differential features of recurrent diseases. Seventeen of 155 patients (11 percent) had more than one episode of bacterial meningitis. There were 26 deaths in the nonrecurrent and none in the recurrent group. Neurological complications occurred in five of 17 patients (29.4 percent) with recurrent disease, and 18 of 138 patients (12.9 percent) without recurrent meningitis. Recurrent meningitis was more frequent in younger persons and males. Patients with recurrent disease were more likely to have an upper respiratory infection, to be hospitalized early in their illness, and to have positive blood cultures. Although a history of severe head trauma was significantly more frequent in those with recurrent disease (35.3 percent) than in those without recurrences (9.4 percent), this history was often overlooked by the patient even in the presence of cerebrospinal fluid rhinorrhea. Most often the trauma occurred six months or more prior to the initial episode of meningitis. The data suggest that each patient presenting with pneumococcal meningitis should be evaluated for evidence of dural tears or other host defense defects. Controlled data concerning surgical or antibiotic prophylaxis are needed.

Raforth R, Morse R, Edwards LD, Jupa J, Levin S: Tuberculous peritonitis after laparotomy. *Scand J Infect Dis 4:139, 1972*

Four cases are described of tuberculous peritonitis occurring 6 to 10 weeks following laparotomy for unrelated illnesses. Four similar cases from 16 previously reported series of tuberculous peritonitis are also described. The possibility of mechanical activation of old peritoneal or mesenteric granulomas is considered. An incubation period of 4 to 10 weeks from surgery to onset of symptoms or diagnosis is suggested in seven of eight reported cases.

Nephrology

Fries J, Powers R, Kempson R: Late-stage lupus nephropathy. *J Rheumatol 1:57, 1974 (Suppl 1)*

Chronic renal insufficiency in systemic lupus erythematosus (SLE) appears to represent a different clinical syndrome from classical immune-complex SLE glomerulonephritis, with different therapeutic implications. This hypothesis is explored.

Thirteen consecutive patients reaching a stage of renal insufficiency following SLE nephritis are examined, and their late course compared with their early manifestations

of SLE. Comparison of the first year of active nephritis with the late stage, an average of 42 months later, included clinical, serological, laboratory, and pathological findings.

Early active SLE nephritis in these patients was associated with multi-organ disease, positive LE preps (100 percent), high titer fluorescent anti-nuclear antibody (ANA) (1:213), anti-DNA antibody (10/11), low B1C protein (58 mgm percent), low hematocrit (27 percent), mild hypertension (145/90), high normal serum creatinine (1.6 mgm percent), profuse proteinuria, and treatment with high doses of prednisone (65 mg/day) and immunosuppressants (9/13). In contrast, the same patients in the stage of renal insufficiency showed almost no rash, arthritis, or pleurisy, negative LE preps (100 percent), low-titer ANA (1:62, negative in five patients), negative anti-DNA antibody (11/13, low normal B1C protein (83 mgm percent), very low hematocrit (20 percent), severe hypertension (183/117), marked creatinine retention (10.3 mgm percent), decreased proteinuria, and decreased prednisone (17 mg/day) and immunosuppressant (2/13) therapy. Without prior information, SLE could not have been diagnosed in 12 of the 13 patients. Pathology of the late stage showed quantitative differences from early biopsies, with increased amounts of fibrinoid necrosis, vascular findings, and hyalinization, and decreased focal necrosis and proliferative glomerulonephritis. Complement synthesis was moderately impaired in the late stage. Plasma renin activity was increased. Nephrectomy controlled hypertension and congestive heart failure. Therapy for SLE was ineffective and resulted in severe iatrogenic infections.

Hypertensive mechanisms of renal destruction involving the reninangiotensin system may be important in late stages of lupus nephropathy. Progression to renal failure may occur after years of functional stability and in the absence of clinical and laboratory findings of active SLE. Management implications for this late syndrome include reduction of corticosteroid and immunosuppressant therapy, and consideration of bilateral nephrectomy, long-term hemodialysis, and renal transplantation.

Neurology

Garron DC: Huntington's chorea and schizophrenia. *Adv Neurol 1:729, 1973*

It is primarily the prodromal personality changes and psychoses, both of which *may* be more frequent and more severe in Huntington's chorea than in other dementing diseases, which suggest a link to schizophrenia. These personality changes and psychoses may be attributed in part to the specific frontal and more general cortical atrophy associated with Huntington's chorea, which may in turn lead to misdiagnosis. In this connection, it may be noted that it is not unusual for organic neurological syndromes to be misdiagnosed as functional disorders. In one survey, 13 percent were so misdiagnosed (Tissenbaum, Harter, and Friedman, 1951). Parkinsonism was most often misdiagnosed (12 of 30 cases), and, incidentally, also involves disease of the basal ganglia associated with more general cortical atrophy (Klawans and Cohen, 1970). Since neither of these lesions characterize schizophrenia, it is unlikely that the two conditions are linked by processes which affect the same general neural structures in the same way.

Even if some link is involved, such as an alteration in the functioning of the same structures, which in schizophrenia does not lead to a visible lesion, there are at least two reasons that it is unlikely for the link to be genetic. Both of these reasons involve the consideration of schizophrenia as a "forme fruste" of Huntington's chorea. First, Huntington's chorea is accepted as a monogenic dominant trait; therefore, schizophrenia cannot be a partial expression mediated by a subset of genes which, in their totality, result in chorea. Second, as the penetrance of the gene for Huntington's chorea is regarded as complete (Myrianthopoulos, 1966), schizophrenia cannot be regarded as a partial expression based on incomplete penetrance.

Given all of the problems noted, it will be necessary to do systematic longitudinal studies of persons at risk, in order to differentiate demented behavior from nondemented psychotic behavior, and to determine whether the incidence of the latter is unusually

great in Huntington's chorea. Until such studies are carried out, the schizophrenic-like psychoses seen in Huntington's chorea might be best regarded as phenocopies (Davison and Bagley, 1969; Slater and Cowie, 1971).

Neurosurgery

Penn RD, Hagins WA: Kinetics of the photocurrent of retinal rods. *Biophys J 12:1073, 1972*

The shapes of the photocurrent responses of rat rods, recorded with microelectrodes from the receptor layer of small pieces of isolated retinas, have been investigated as a function of temperature and of stimulus energy. Between 27 and 37° C the responses to short flashes can be described formally as the output of a chain of at least four linear low-pass filters with time constants in the range 50 to 100 msec. The output of the filter chain is then distorted by a nonlinear amplitude-limiting process with a hyperbolic saturation characteristic. Flashes producing ∽ 30 photons absorbed per rod yield responses of half-maximal size independently of temperature. The maximum response amplitude is that just sufficient to cancel the dark current. The rate of rise of a response is proportional to flash energy up to the level of 10^5 photons absorbed per rod, where hyberbolic rate saturation ensues. The responses continue to increase in duration with even more intense flashes until, at the level of 10^7 photons absorbed per rod, they last longer than 50 min. The time-courses of the photocurrent and of the excitatory disturbance in the rod system are very similar. The stimulus intensity at which amplitude saturation of the photocurrent responses begins is near that where psychophysical "rod saturation" is seen. An analysis of these properties leads to the following conclusions about the mechanism of rod excitation. (a) The kinetics of the photocurrent bear no simple relation to the formation or decay of any of the spectroscope intermediates so far detected during the photolysis of rhodopsin. (b) The forms of both the amplitude- and rate-limiting processes are not compatible with organization of rhodopsin into "photoreceptive units" containing more than 300 chromophores. Even at high stimulus intensities most rhodopsin chromophores remain connected to the excitatory apparatus of rods. (c) The maximum rate of rise of the photocurrent is too fast to be consistent with the infolded disks of a rod outer segment being attached to the overlying plasma membrane. Most of the disks behave electrically as if isolated within the cell. (d) Control of the photocurrent at the outer segment membrane is not achieved by segregation of the charge carriers of the current within the rod disks. Instead, it is likely to depend on control of the plasma membrane permeability by an agent released from the disks.

Penn RD, Hilal SK, Michelsen WJ, Goldensohn ES, Driller J: Intravascular intracranial EEG recording: Technical note. *J Neurosurg 38:239, 1973*

Spontaneous and evoked electrical activity from the basal and medial areas of the brain not accessible in routine electroencephalography (EEG) has been recorded with single and bipolar electrodes in intracranial vessels of baboons. The report also demonstrates intracranial intravascular EEG recording in man.

Oncology

Perlia CP: The problems of drug treatment in breast cancer. *Semin Drug Treat 3:87, 1973*

The magnitude and problems of mammary carcinoma in its various stages has not significantly changed in the past 10 years. There is as yet no single best treatment. However,

a better understanding of the biology of the tumor, as well as the host and newer pharmacokinetic data of different drugs, promises to improve therapeutic results in the near future.

Combination of a number of effective drugs has added significantly to our knowledge of the treatment of this common cancer. The real and relative indication and merits of such combinations still need further properly randomized studies before being used or advocated indiscriminately. The clinician treating only an occasional patient with advanced breast cancer has to rely mainly on an adequate inventory of the patient's disease, and proper analysis of factors known to influence the course of this neoplasia. Alternatively, he has the option to participate in an increasing number of national and regional cooperative studies. This should allow for improved documentation of the disease, more meaningful interpretation of the various therapeutic modalities and above all, no disadvantage to the patient.

Rossof, AH, Slayton RE, Perlia CP: Preliminary clinical experience with *cis*-diamminedichloroplatinum (II) (NSC 119875, CACP). *Cancer 30:1451, 1972*

Thirty-one patients with metastatic cancer were treated with *cis*-diamminedichloroplatinum (II), CACP, in dosages ranging from 7.5 to 200 mg/m² BSA per course. Twenty-two patients received more than one course. Toxicity to the initial course of CACP, up to 90 mg/m² BSA, was minimal and transient in most patients. At higher dosage levels or following repeat courses, the drug-related toxicity was more severe. Drug-related toxicity was more severe in patients with abnormal excretory tracts. The most common and earliest side effects were nausea and vomiting. Hyperuricemia commonly occurred shortly after administration of CACP. A dosage-dependent, generally transient, nephrotoxicity was noted within the first 10 days after a course of CACP. Moderate leukopenia and thrombocytopenia, as well as a progressive normocytic anemia with marrow erythroid hypoplasia, were observed as late as three to four weeks after injection of this agent. Audiologic impairment above the frequency range of normal speech was detected by audiometry. Objective tumor regression was seen in five patients, four of whom experienced moderate-to-severe toxicity.

Wilbanks GD: A selective review of experimental studies in cervical carcinoma. *Cancer Res 33:1379, 1973*

With various human clinical, epidemiological, and experimental data together with basic carcinogenesis experimentation, a working hypothesis of the development of cervical cancer is presented. Initiation may involve a carcinogen (perhaps herpesvirus type 2) altering the susceptible metaplastic cervical cell that is active in adolescence and during pregnancy. Promotion by factors perhaps related to coitus or to the continued metaplastic process in a field of abnormally mitosing cells allows for selection of a clone of cells with the characteristics of unlimited growth and invasion.

Ophthalmology

Herman SJ, Hughes WF: Recurrence of hereditary corneal dystrophy following keratoplasty. *Am J Ophthalmol 75:689, 1973*

Patients with hereditary corneal dystrophy were re-examined 2½ to 15 years following uncomplicated penetrating corneal transplantation to determine possible recurrence of the original dystrophy in the graft. Recurrence was noted in the eye of one patient with granular dystrophy. In 11 of 15 eyes with lattice dystrophy, recurrence was noted, and in three others probable recurrence was seen, while one eye showed no recurrence after

two and one-half years. No definite recurrences were found in seven eyes operated on for macular dystrophy. Because the donor is gradually replaced by host tissue with a genetic defect, recurrence of the hereditary dystrophy in the graft would be logically expected.

Huckman Ms, Haas J: Reversed flow through the ophthalmic artery as a cause of rubeosis iridis. *Am J Ophthalmol 74:1094, 1972*

In two cases of internal carotid artery occlusion with rubeosis iridis and neovascular glaucoma, carotid arteriography demonstrated retrograde collateral circulation through the ophthalmic artery on the side of the involved eye. This suggests that occlusion of the carotid artery may not be the primary cause of the neovascular glaucoma; instead, neovascular glaucoma in these two cases—and perhaps others—may be the result of an ophthalmic artery "steal" phenomenon. The presence of neovascular glaucoma in patients with surgically corrected carotid-cavernous fistula seems to support this theory.

Pathology

Clasen RA, Hartmann JF, Coogan PS, Pandolfi S, Laing I, Becker RA: Experimental acute lead encephalopathy in the juvenile rhesus monkey. *Environ Health Perspect, p. 175, May 1974*

Lead subacetate (0.5g) and 1000 units of vitamin D were given three times a week to four newly-weaned rhesus monkeys. In addition, two animals received only the vitamin D. The poisoned animals had an increase in the urinary excretion of δ-aminolevulinic acid, an elevated content of lead in the blood, and a fall in hemoglobin concentration. Between 6 and 18 weeks the animals suddenly developed ataxia, nystagmus, generalized weakness, and convulsions. At this time the animals were killed by perfusion of fixative and the brain prepared for light and electron microscopic studies. Definite morphological evidence of disease was confined to the central nervous system, except for one animal which showed the characteristic renal inclusions of lead poisoning. All animals showed PAS-positive globules associated with blood vessels and an exudative edema involving the white matter of the cerebral hemispheres and cerebellum. Ultra-structurally, this appeared as a granular precipitate within an expanded extracellular space. Alterations of nerve fibers were not seen in the white matter but axonal swelling was observed in the cerebral cortex. The perikaryon and neuropil appeared normal. The control animals showed no significant cerebral changes.

Clasen RA, Hartmann JF, Starr AJ, Coogan PS, Pandolfi S, Laing I, Becker R, Hass GM: Electron microscopic and chemical studies of the vascular changes and edema of lead encephalopathy. *Am J Path 74:215, 1974*

Lead encephalopathy was induced in suckling rats by administering lead to the mother. The brains were studied by light and electron microscopy, and the results were compared with observations in the human disease as well as in cases of cerebral ischemia in children. In their severe forms, both human and experimental lead encephalopathies are characterized by exudative extracellular edema and perivascular PAS-positive globules. The latter consist of osmiophilic non-membrane-limited cytoplasmic inclusions located, in the rat exclusively and in the human predominantly, in perivascular astrocytes. Intervascular strands are also found in both forms of the disease. In the rat these consist of basement

membrane surrounding endothelial cytoplasm. Chemically, experimental lead encephalopathy with morphologically demonstrable edema is associated with an increase in brain water, sodium and serum albumin. Relative to the serum concentration, the increase in water is disproportionately greater than the sodium or albumin. There were no demonstrable changes in chloride or potassium.

Clasen RA, Hindo WA, Pandolfi S, Laing I: The role of necrosis and inflammation in the response of cerebral edema to steroids. *In: Steroids and Brain Edema, Ed by H. J. Reulen and K. Schürmann, 1972, Berlin, Heidelberg, New York, Springer-Verlag, pps. 157-166*

The effect of steroids on the edema associated with lesions induced by focal cerebral freezing in monkeys was assessed. The animals were sacrificed 48 hours after injury. In one group treatment was begun 48 hours prior to injury, and in a second group treatment was begun after injury but the lesion size was reduced. The degree of edema was assessed through measurements of changes in the concentrations of tissue water, sodium, chloride, potassium, and iron and by the increase in weight of the damaged hemisphere. In addition to this, the uptake of serum albumin and Evans blue also was measured. No indication of any effect on edema in either group was found.

The degree of edema in the brains of patients with unilateral metastatic tumors was assessed through measurements of hemispheric weights. It was found that those patients having a favorable neurological clinical response to steroids at the time of death had less edema than those who did not. Histologic changes in the brains of such patients were analyzed. It was found that lesions from those patients who were not responding to steroids at the time of death showed significantly more inflammation than those who were responding.

An attempt is made to define the relative roles of necrosis and inflammation in the response of cerebral edema to steroid management. It is concluded that the presence or absence of cellular inflammation is the determining factor in this response.

Clasen RA, Pandolfi S, Casey D Jr: Furosemide and pentobarbital in cryogenic cerebral injury and edema. *Neurology, Minn 24:642, 1974*

The effects of furosemide and pentobarbital on the edema associated with cryogenically-induced cerebral lesions in the rhesus monkey were quantitatively measured. Both drugs caused a decrease in the increments of water, sodium, and chloride in the damaged hemisphere. In addition, the pentobarbital was associated with a decrease in the uptake of serum protein. The effects of the two drugs were not additive. It is proposed that furosemide be given a clinical trial in the treatment of human cerebral edema.

Clasen RA, Pandolfi S, Casey D Jr: Reserpine in experimental cerebral edema: further observations. *Neurology, Minn 24:594, 1974*

Focal areas of hemorrhagic necrosis were produced in the brains of anesthetized rhesus monkeys by freezing through the intact skull. Half of the animals were given reserpine beginning one hour after injury, and all animals were killed 24 hours after injury. The edema associated with the lesions was assessed by various methods. The animals receiving reserpine showed significantly less edema than controls as judged by water changes in the damaged hemisphere and significantly less hemorrhage in the lesion as determined from changes in tissue iron. This was not accompanied by a decrease in serum albumin

uptake but the uptake of Evans blue was diminished. Body temperature and systemic blood pressure were decreased in the reserpine-treated animals.

Scott RA, Henson DE, Lesak A, Turner RJ, Malikova S, Hass GM: Relations between metabolic increase of plasma free fatty acids and the occurrence of arteriosclerotic thromboarteritis in rabbits. *Am J Path 70:209, 1973*

Rabbits maintained for several weeks on a regimen of modest amounts of vitamin D and dietary cholesterol were placed in three groups in accordance with their response to repeated subcutaneous injections of nicotine in mineral oil. The group that had the greatest increase in plasma free fatty acids (FFA) following nicotine injections gradually developed, over a period of about 12 weeks, severe calcific atheroarteriosclerosis with peripheral thromboarteritis. Those that had a moderate increase in plasma FFA following nicotine injections developed calcific atheroarteriosclerosis but no thromboarteritis. Those that had the least increase in plasma FFA following nicotine injections developed no arterial lesions. Comparable or much greater increases in plasma FFA occurred in rabbits on the vitamin D-cholesterol regimen when adrenalin, ACTH or heparin was injected rather than nicotine. These animals did not develop calcific atheroarteriosclerotic thromboarteritis or any other lesions which could be correlated with the increased levels of plasma FFA. Inasmuch as nicotine, vitamin D or dietary cholesterol in the amounts used were innocuous when used alone, the interactions between the effects of at least these three factors need to be known in individual animals before the pathogenesis of the calcific atheroarteriosclerotic lesions with thrombosis can be eventually understood.

Pediatrics

Hyde JS: Cromolyn sodium in childhood Asthma. *Hosp Pract, 111, 1974*

Clinical trials have shown that this agent decreases frequency of asthmatic attacks, makes possible reduced concomitant medication, and improves pulmonary function and other parameters of childhood asthma in about four fifths of patients. But it is a prophylactic, not a symptomatic treatment, and does not abolish the need to determine the source of the asthma and provide adequate symptomatic protection against its manifestations.

Sadove, MS, Schmidt G, Wu H-H, Katz D: Indirect blood-pressure measurement in infants: a comparison of four methods in four limbs. *Anesth Analg (Cleve) 52:682, 1973*

The Korotkoff method, oscillometry, and the flush technic constitute the three principal conventional approaches for measurement of blood pressure in the neonate and infant. In a comparison of these methods with the newer ultrasonic approach in the same population, all four methods demonstrated acceptable reproducibility, as determined by agreement between right and left arm measurements. Significantly, however, ultrasonic measurements were routinely obtainable, while it was frequently impossible to obtain readings by conventional methods. Korotkoff brachial sounds were audible in only half the series, and leg measurements even less often. The flush and oscillometric technics are inherently unsuitable for diastolic determinations.

The ultrasonic method yielded more leg blood-pressure measurements than did the three conventional methods and was the only method that provided diastolic leg pressures. Application of this technic in a relatively large series of healthy neonates and children yielded the somewhat startling finding that leg pressures exceeded arm pressures for approximately the first week of life, after which they remained essentially equal.

Curtin JW: Basic plastic surgical techniques in repair of facial lacerations. *Surg Clin N Am 53:33, 1973*

In the treatment of craniofacial trauma an evaluation of the *entire* patient must be made in order to establish proper priority of management.

An adequate airway must be established, shock corrected, and a condition of adequate anesthesia (local or general) achieved before cleansing, inspection and repair of facial lacerations.

The greatest deterrent to wound infection is a healthy viable wound produced through cleansing, atraumatic and meticulous handling of the tissues, and obliteration of all potential spaces by accurate approximation of all layers of tissue.

Early surgical closure is emphasized. Descriptions of management of superficial, deep, and compound lacerations and avulsions as well as enumeration of all important deep structures of the face encountered are included.

A good final result in this most important anatomical area can be promised by attention to detail in a region in which a rich blood supply is our greatest ally.

Curtin JW: Changing concepts in the treatment of craniofacial anomalies. *Cleft Palate J 9:269, 1972*

The American Cleft Palate Association had its beginnings in 1943 with the objectives of stimulating specialistic and public interest, and more exact knowledge and improved practice of the science and art of rehabilitation of persons with a cleft palate and associated deformities of the mouth and face.

Later there were formed throughout this country coordinated groups of specialists in what became known as the Cleft Palate Team approach to the study and rehabilitation of the cleft-lip and cleft-palate patient. Such multidisciplinary teams increased from one in 1946 to 46 in 1955 and more recently have expanded to 138 teams staffed by approximately 2500 professionals.

Over the past decade there has been increasing concern for congenital malformations aside from those of pure cleft lip and cleft palate. The thalidomide tragedy made us terribly conscious of environmental factors and their effect on the ecology of the fetus. Large university cleft palate centers see their interests broadening to include genetics, teratology and craniofacial biology.

It is for those reasons that a plea is made to include other disciplines in the Association so that interests, energies and research once expended toward the correction of cleft lip and palate are now being used to support the study and correction of craniofacial anomalies.

Monroe CW, Ogo K: Treatment of micrognathia in the neonatal period; report of 65 cases. *Plast Reconstr Surg 50:317, 1972*

Sixty-five infants with micrognathia have been seen in the Children's Memorial Hospital in a 20-year period. Their records have been carefully studied to elucidate the major associated anomalies and to learn what sort of management gave the best results. The following items stand out:

1. Cardiac anomalies are the most frequent and severe complication of micrognathia (21.5 percent of the patients). Ten of the 14 cardiac patients died, though in only six was the death thought to be due to the cardiac problem.
2. There were 14 deaths in all (21.5 percent). Six of these were due to cardiac problems, the other 8 to aspiration or pneumonia, or both.
3. Tracheostomy was done in nine patients, with two deaths. The average period of time the tracheostomy tube was worn was 19.2 months.

4. It seems likely that at least five of the seven deaths in patients without tracheostomies, from aspiration or pneumonia, might have been prevented by a more liberal use of tracheostomy.

Radiology

Chung-Bin A, Wachtor T, Masek G, Hendrickson FR: Patient information retrieval using a medium sized computer. *Presented at the Scientific Proceeding, 58th Scientific Assembly and Annual Meeting, The Rad Soc, November 26-December 1, 1972*

Our Department of Therapeutic Radiology has operated a user-oriented patient information retrieval program called RTRAN (Retrieval Translation). This system consists of 80-880 characters of data per patient record stored on magnetic tape updated and retrieved using an 1800 IBM computer.

Programs are all written in FORTRAN. An effective form of buffering 1/0 is achieved to make retrieval time reasonable. The patient records are stored in semi-alphabetic order to speed up the lengthy process of updating.

The RTRAN language consists of an arbitrary number of English sentences. The formulation of an RTRAN sentence is QUESTION & RESPONSE. The QUESTION portion is constructed from seven operators separated by the connectives AND, OR. The QUESTION defines a subset of the data base. The RESPONSE defines action to be taken on that subset. In addition to the commands PRINT and PUNCH, the RESPONSE portion includes the commands PRINT NSDE and TABULATE. The TABULATE command, for example, produces a ten-year survival table. This form of retrieval can be quite oriented to the user's needs.

The simplicity in the use of this program to periodically generate a list of patients for particular sites and stages can be used to improve subsequent care and generate up-to-date survival tables.

English JT, Patel SK, Flanagan MJ: Association of pheochromocytomas with brown fat tumors. *Radiology 107:279, 1973*

Pheochromocytomas and tumors of brown fat (hibernomas) have occasionally been reported to occur in the same patient. A single such case has recently appeared in the radiologic literature. The present report concerns the angiographic findings of a patient who had both a functioning intrathoracic pheochromocytoma and a perirenal brown fat tumor.

Pheochromocytomas are known to be associated with multiple endocrine adenomas and various metaplasias of the neural ectoderm: neurofibromas, tubular sclerosis, and neurohemangioblastomas, etc. An additional association of pheochromocytoma with brown fat tumors has been proposed since the repeated occurrence of these two relatively rare conditions together is unlikely on a random basis. Awareness of such an association is of value because in most of the reported cases, the presence of the hibernoma obscured the diagnosis of pheochromocytoma. Since the present case supports the existence of such an association, a review of the literature has been undertaken.

Huckman MS, Fisher MS: Roentgenographic signs of tumors of the greater omentum. *Cancer 33:1526, 1974*

Analysis of two new cases and a review of the literature suggest that primary tumors of the greater omentum are distinguishable by upward and posterior displacement of the stomach, and downward and anterior displacement of the transverse colon by an extrinsic mass around which loops of small bowel are usually displaced. Clinical findings and operative management are discussed.

Petasnick JP: Congenital malformations of the ear. *Otolaryngol Clin North AM 6:413, 1973*

Malformations of the ear comprise an important group of congenital anomalies of the head and neck exceeded in frequency only by cleft lip and palate. Malformations of the external ear are the most common, however. In recent years there has been an increased awareness of inner ear malformations as a cause of sensorineural deafness. Direct otoscopic examination of the middle ear is impossible in the presence of severe stenosis or atresia of the external auditory canal, and tomography is the only reliable non-surgical means of evaluating the middle and inner ear. The structures of the middle and inner ear can be clearly delineated and the pathologic anatomy precisely defined. Malformations of the temporal bone have been classified according to their involvement of the external auditory canal, middle ear, and inner ear and representative examples of each have been demonstrated.

Sondag TJ, Patel SK, Petasnick JP, Chambliss J: Hypernephromas with massive arteriovenous fistulas. *Am J Roentgen 117:97, 1973*

Four cases of hypernephroma with massive arteriovenous fistula are reported.

A review of the literature together with our cases shows that cardiovascular manifestations are not always associated with this entity at the time of discovery, as has been previously stressed in the literature. The factors thought to be responsible for this are mentioned.

The clinical, roentgenologic, and pathologic features of our four cases are discussed.

Surgery

Doolas A, Economou SE, Gilchrist RK: Prophylactic surgery for diverticular disease of the colon. *Contemporary Surg Nov/Dec, 1972*

As the aged population increases, so does the incidence of diverticulitis. Thus the question of when to operate arises more and more frequently.

In the past 30 years there has been an increasing trend to operate early, since surgery for the complications of diverticulitis is accompanied by a high mortality rate. Our experience confirms this: 13 percent of our patients treated on an urgent or emergency basis died.

Our findings also attest to the unpredictability of the disease: 15 patients with a history of *mild* diverticulitis and 23 with *no history* of diverticulitis required surgery on an urgent or emergency basis. This suggests that greater efforts must be made to detect the symptoms of diverticulitis in patients with vague bowel complaints.

The accepted mortality rate for patients undergoing elective surgery, on the other hand, is one to two percent. None of our patients who had elective surgery died. Morbidity, in terms of days spent in the hospital, is also greatly reduced for elective patients since they do not require a colostomy.

Most of the patients we treated electively had had either multiple mild episodes of diverticulitis or severe diverticulitis that became quiescent on medical therapy. We believe, however, that surgery should also be considered for middle-aged patients with x-ray evidence of severe diverticulosis with spasm and for patients with x-ray evidence of a fixed deformity from diverticulitis. In the absence of *any* previous symptoms, the initial complications of diverticulitis can be devastating.

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CELLULAR AND MACROMOLECULAR ENGINEERING— A VITAL NEW APPROACH TO DISEASE

ROBERT A. GOOD

ABSTRACT. During the past thirty-one years, my students and I have had the privilege to participate in and contribute to the extraordinary growth of immunobiology in medicine. We have tried to take advantage of Nature's experiments. We have tried to take the questions focused by the problems presented to us at the bedside to the developing science in the laboratory, and to utilize the developing methods of modern technology to delineate and understand the basic principles of immunobiology. We have tried to use a tripod of the issues focused in the clinic and by ontogenic and phylogenetic studies to achieve this understanding. Herein are reviewed a few of the crucial issues in my own personal past that have helped focus and develop this field, and a consideration of certain current incisive experiments of Nature which are guiding our present investigations. The rapidly accumulating knowledge of the structure and function of the immune systems is guiding the way to new approaches of diagnosing and manipulating disease processes. A combination of macromolecular and cellular engineering, ultimately extending to and manipulated via small molecule pharmacology, may well become the new way of approaching innumerable diseases. Surely the thought processes of modern immunobiology will continue to be at the center of the medicine of the future.

It is really a pleasure to return to the Rush-Presbyterian-St. Luke's Medical Center and to see the extraordinary developments and progress that you have made since I visited here just a few years ago. I have always felt a welcome guest here, but now I feel like one of the family. It is a particular privilege to salute with you the leadership and guidance that is represented by Dr. Thomas J. Coogan, Sr., a great pioneer in the development of this academic endeavor, and also to salute with you the establishment of the Chair in Immunology, under the professorship of my former student and associate, Dr. Henry Gewurz.

A Department of Immunology—that's neat! This is one of the first in America. There are other departments of immunology in the making at Buffalo and at the Mayo Medical School, and it is nice to know that there is such a department in this rapidly developing medical center. I think that you are so wise to be one of the first American schools to follow the World Health Organization's recommendation to establish a department of immunology. In this respect, you are leading the way, and will be followed by most of our medical schools. This does not mean that all immunobiology should be in the Department of Immunology. It cannot be; it has to be in every nook and cranny of the medical

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Presented at the commemoration of the opening of facilities of the Department of Immunology and assignment of the Thomas J. Coogan Chair of Immunology, January 8, 1974, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

center. But a focus in a department of immunology is essential for the fullest development and most crucial scientific progress in this field. Dr. Gewurz is already a major contributor, and I am absolutely certain from my experience this morning with what I have to consider my intellectual grandchildren that he is going to be even more of a contributor and leader in this maximally productive environment.

This was a wonderful morning—there were so many exciting new findings, directions and turns which the young people showed us that I almost would like to start a postdoctorate fellowship myself! But I have been at this business 31 years. I started in immunology at the University of Minnesota in 1942, and made my first discovery there in 1943.[1] It is interesting to look back and think about what immunology was in those days. We knew about antibodies, but we knew nothing of the chemistry of the molecules involved in the immunological process. Oh yes, we had already had Tiselius and Kabat's contribution; antibodies were in the gamma globulin fraction.[2] Since that time, of course, we have become aware of the entire structure of most of these molecules.[3] We knew nothing of the cells that are involved in the immunological process, and there were whole organs involved in immunity, like the thymus and the spleen, whose functions were completely enigmatic. Thus, we have seen in this 31-year period an extraordinary development in the field of immunobiology. This is part of a scientific revolution in medicine.

Today there is so much of the immunobiologic component in this revolution that we see immunology already almost taking over major branches of clinical medicine. Rheumatologists, by and large, consider themselves applied immunobiologists. Nephrologists have been using the immunobiologic tools in an immunological dissection of the various chronic and acute renal diseases. I cannot think of the hematologists trying to address the major issues of hematology without immunobiologic tools, and immunologic mechanisms are very important in the pathogenesis of most hematological diseases, even pernicious anemia. One may not regard immunobiology as a foundation of endocrinology, but the revolution in endocrinology also has utilized the precision and sensitivity of the immunobiologic assays that were introduced so forcefully in that field by the late Saul Berson.[4] Dermatology and neurology are also areas in which immunobiologic incursion is occurring every day. In surgery too we have seen an immense change, and more and more surgeons are preparing to be, or have already become, full-fledged immunobiologists. What about psychiatry? I am not sure, but it seems to me that there is a strong likelihood of learning really important principles about how we think and how we behave, from the study of a system which has anticipatory behavior, adaptive behavior, and memory. It is predictable that in psychiatry too these principles will play a major role.

I am convinced that the extraordinary revolution we have seen over the past 31 years is simply a beginning. It is just like the first crack of the shell in the delivery of a bird or a reptile. Over this 31-year period, my students and I have been privileged to participate in this extraordinary growth of immunobiology in medicine. Opportunists, we have tried to take advantage of Nature's experiments. We have tried to take the questions focused by the problems presented at the bedside to the developing science in the laboratory, and to utilize the developing methods of modern technology in delineating and understanding the basic principles of immunobiology. We have tried to use a tripod of the issues focused in the clinic, and by ontogenetic and phylogenetic studies to achieve this understanding. We think that this is a powerful approach, and recommend it to you.

I would like to review briefly a few of the crucial issues in my own personal past that have helped focus and develop this field, and to consider some incisive experiments of nature. I started in immunobiology because a very aggressive surgeon, Dr. Fred Kolouch, came to see me in my

laboratory, where I was doing some rather desultory work on the early pathology of a virus infection in the central nervous system. He said to me, "Why don't you do something important? Why don't you help me with *my* research?" And I listened to his story. It was most fascinating because it began in the clinic and concerned a patient with subacute bacterial endocarditis whom Dr. Kolouch had followed to autopsy. In this patient, infected with *Streptococcus viridans,* he had observed an extraordinary accumulation of plasma cells in the bone marrow and in the spleen.[5] He was influenced by Bing and Plum,[6] who, the year before in Copenhagen, had seen another experiment of nature, the association between plasma cells and the accumulation of gamma globulin in the serums of three of 11 or 12 patients with aplastic anemia. Bing and Plum had made the audacious extrapolation that perhaps those plasma cells produced the globulin accummulating in the circulation. I worked with Kolouch, to try to interpret his natural experiment in the laboratory. I was able to make some small contributions toward his thesis and began to communicate, in the early 1940's, with a small group of "plasma cell hunters" who were really outcasts of the cellular immunologists. Fagraeus was in that group and made a major contribution with her beautiful studies involving dissection of small pieces of spleen. She found that the plasma cell-rich areas produced gamma globulin, whereas the plasma cell-poor, lymphocyte-rich areas did not.[7]

These interests led me to the Rockefeller Institute, not yet a University in those days, where I met Henry Kunkel—*there* was a young man with fire in his belly! He really wanted to study the immunochemistry of the relationship between myeloma proteins, another very interesting experiment of nature, and normal gamma globulin. I wasn't too interested in Henry's work, but I was a plasma cell-hunter, and was able to obtain for him some serum on which he could do his analyses. This[8] opened the Pandora's box which has led us now, as you saw a few weeks ago in Science[9] to the complete molecular definition of IgG on the one hand and IgM on the other. Kunkel's student, Gerald Edelman, was awarded the Nobel Prize for defining the structure of IgG, certainly a major contribution. Now the molecular analysis of IgA is half-completed, and even the J chains and the transport piece are purified and in the process of being sequenced—a job that should be completed this next year.

However, I wasn't interested in Henry Kunkel's problem. It was the myeloma *patients,* not the myeloma *protein,* that interested me. These patients, whom I saw on David Barr's service at the New York Hospital and Memorial Hospital, were suffering from one infection after another. Their infections were caused particularly by virulent, encapsulated pathogens, including the pneumococcus, streptococcus, and *Hemophilus influenzae,* and by *Pseudomonas aeruginosa.* Infections with these organisms were causing the problems which we saw in the patients with myeloma, the same patients from whom I drew blood which helped Henry Kunkel on the way to analysis of the immunoglobulin structure.

Let me repeat, I had not come to work for Henry Kunkel. I really had come to the Rockefeller to work with Mac McCarty, and I thought I could please Dr. McCarty by crystallizing the C-reactive protein. (In fact, one reason this morning was so delightful is the intensive current work here on C-reactive protein. It was wonderful to get back into the field I left so long ago.) McCarty previously had crystallized the C-reactive protein from streptococcal effusion fluids,[10] but by the time I arrived in New York in 1949, these effusion fluids rarely were seen; penicillin had taken care of that job, so I had to search for another source of C-reactive protein to crystallize. I found it in the effusion fluids of patients with Hodgkin's disease. I could obtain large amounts of effusion fluids from these patients, and thus repeat McCarty's contribution of crystallizing C-reactive protein in order to help define it.

But I wasn't really interested in McCarty's problem either; I was interested in the fact that these patients with Hodgkin's disease, from whom I drew the effusion fluid, were patients who had many infections. They had infections with the tubercle bacillus, atypical acid-fast organisms, fungi including the cryptococcus, and viruses including members of the herpes and pox groups.

We began to realize that in these two experiments of nature, we were observing a dissection of the microbial universe which was putting together strange bedfellows, in that patients of the two groups had trouble resisting distinctly different spectrums of infections.

Studies of the immunological defects in the patients with Hodgkin's disease, initiated in a very definitive way by Schier,[11] soon revealed that these patients had defects in the cell-mediated or delayed-type hypersensitivity reaction. We showed, with Kelly, that they also had trouble rejecting skin allografts.[12] However, they generally had increased amounts of serum gamma globulin and formed antibodies very well to most of the antigens with which they were challenged.

By contrast, the patients with multiple myeloma could not form antibodies very well, even though they had large amounts ("spikes") of gamma globulin and immunoglobulin. Yet, they had normally intense delayed-type hypersensitivity reactions, and could reject both first- and second-set homografts very well.[13] Thus, these two natural experiments had focused a counterpoint for us.

Bruton's discovery of agammaglobulinemia clarified this.[14] Patients with agammaglobulinemia of the X-linked infantile type had no antibodies, and could not form antibodies which could be measured in minute quantities (1×10^{-5} μg/ml antibody nitrogen) to even the most intensive antigenic stimulation. They lacked plasma cells and were unable to form germinal centers. However, they did not lack immunity. They could resist infections with the tubercle bacillus, histoplasmosis and other fungi, and many viruses perfectly well. They had sufficient numbers of lymphocytes in the circulating blood. The deep cortical areas of their lymph nodes were filled with perfectly normal lympho-

Which agents were inducing the infections in these patients? The very organisms which were infecting the patients with multiple myeloma: pneumococcus, streptococcus, *H. influenzae* meningococcus and *P. aeruginosa*. Strange bedfellows, drawn together by the fact that ability to form antibodies is critical to how one resists and recovers from certain kinds of infection. The agammaglobulinemic patients could resist numerous other infections quite well, including those induced by viral agents, although certain viruses caused more trouble in agammaglobulinemic than in normal individuals.

We thus observed that certain diseases of man serve to dissect the microbial universe, and in 1957 I began to write about there being two major kinds of immunity systems.[16]

We were then confronted with another experiment of nature: a man who was in good health until his middle fifties, when he began to develop multiple types of infections. He had a broadly-based immunodeficiency disease associated with the development of a huge tumor in his mediastinum. Removal of that tumor (a benign stromalepithelial thymoma) by my colleague Dr. Richard Varco did not correct the immunologic defect.[17] However, in this experience nature again was not completely unkind. She put together two very unusual diseases, a primary immunodeficiency disease (then the second known case of so-called acquired agammaglobulinemia) and a rare tumor of the thymus. This suggested to us that there must be some relationship between the thymus and immunity.

We turned to the laboratory to study this association, with a major assist from Bruce Glick. Then a graduate student, Glick discovered that the thymus-like bursa of Fabricius, a lymphoid organ located at the posterior end of the gastrointestinal tract in the chicken, was essential for the development of the immuno-

logical capacity in that species.[18] Chickens bursectonized in the newly hatched period, but not as adults, failed to develop the ability to form antibodies in response to antigenic challenge. This experience prompted us to remove the thymus of the newborn animal (we first did so in the rabbit), and our first discovery concerning this organ showed that an animal thymectomized in the immediate neonatal period could not make antibody to bovine serum albumin nearly as well as could normal controls.[19] We also quickly found that mice which had been thymectomized very early in life did not express delayed-type hypersensitivity, did not reject allografts of skin very well, and could not induce graft-versus-host reactions although they were very susceptible to such reactions.[20]

After extensive further experimentation, including a discovery parallel to ours in England by a group coming at the problem from a different direction,[21] it was possible to associate the bursa of Fabricius with the formation of plasma cells, germinal centers and immunoglobulins, and the thymus primarily, with a capacity to develop a population of lymphocytes which now are called T cells. T cells are quite distinct from that population of cells which differentiates into the plasma cells which now are called B lymphocytes. We then knew that there were two immunity systems.[22]

Today we can quantify the cells of these two systems in the circulating blood of healthy individuals using four separate methods. It is possible easily to define the T lymphocyte. These are cells in the circulating blood that have no readily demonstrable immunoglobulin at their surface. They are "bald-headed" cells, with a smooth exterior when examined with a scanning electron microscope which yields a more or less three-dimensional view of the exterior of the cell surface.[23] They have a display of antigens at their surface which, in the mouse, represents the expression of at least 11 separate reasonably well-defined genes.[24] In man, they adhere to sheep erythrocytes at 4°C[25] and react with antisera made against T cell specific antigens. These cells comprise some 60 to 75 percent of the circulating lymphocytes.

Counterposed to them are the B lymphocytes, on the surface of which one can readily demonstrate the various immunoglobulin classes. Cells bearing IgM are predominant, but one also finds cells displaying IgG, IgA, IgD, and IgE. These are the "hairy lymphocytes" which have a very complex surface as seen with the scanning electron microscope.[23] They also have receptors on their surface for aggregated IgG immunoglobulin, as well as for the third component of complement. Each of the characteristics cited above provides a way in which T cells, on the one hand, and B cells, on the other, can be quantified,[26] and these methods agree beautifully with each other.

In healthy individuals the numbers of recognizable T and B cells usually account for almost all of the circulating lymphocytes. There may be minor gaps in normal individuals, but the major gaps have been in patients with certain diseases. Some patients have lymphocytes in the circulation which cannot be defined either as B or as T cells, while other patients have lymphocytes with only *some* of the markers of B cells or of T cells.

Such variation has permitted the development of a very exciting new pathology with respect to malignancies of the lymphoid system. Dr. Rappaport here in Chicago had developed a lovely classification for solid tissue non-Hodgkin's lymphomas,[27] to which he was able to woo most of the world's pathologists; now that it is generally accepted, it has to be set aside because it is wrong. It may have been useful, but the new pathology allows one to define the cells of which these tumors are comprised by objective immunologic methods in these extraordinary ways and thus permits agreement as to their nature. The immunologic methods now developed have provided simple means of identifying a malignancy of the lymphoid tissue as consisting of B, T or even M cells (the M cells being those of the monocytic-histiocytic variety).[28] Using this new pathology, deficits of circulating T or B cells are

found to occur when the normal functions of the immunity system are deviated or compromised because of a monoclonal expansion of a given cell population. Some of the patients with acute lymphatic leukemia can be defined as having a malignant expansion of their T lymphocytes.[29] There is impeccable evidence that the leukemias that begin in the thymus of the AKR strain of mice are comprised of T lymphocytes, because they bear the characteristic thymic-specific (TL) alloantigen.[30] This alloantigen characterizes these lymphocytes only at that stage of their differentiation when they are present in the thymus.

By contrast, the work of many investigators[31–34] has shown that in almost every instance of chronic lymphatic leukemia there is a monoclonal expansion of the B lymphocytes. Usually these B lymphocytes have IgM immunoglobulin on their surface, although a few with IgG or IgA have been defined. Further, in patients with non-Hodgkin's solid tissue lymphomas, as in chronic lymphatic leukemia, very new and exciting information has identified between 66 and 80 percent of these pathological entities as representing a monoclonal expansion of the B-cell population; yet this disease may present in a manner very distinct from that of chronic lymphatic leukemia. It often is called histiocytic disease, but of course it has no relationship to the histiocyte. I presume that the leukemias of T-cell origin also represent monoclonal expansions, because in several instances the cells have been grown and maintained in culture and they differ very strikingly from one another.[35]

We therefore are now seeing a new pathology based on the immunologic analysis of the cell surface. This may well herald an extraordinary development not limited to tumors of the lymphoid population, but perhaps also providing a new approach to identifying the point of deviation or differentiation of the monoclonal expansion which occurs in a variety of other malignancies.

These ways of defining T and B cell structure and function also permit definition of the immunodeficiency diseases in cellular as well as in molecular terms. Already we are able to utilize this information to achieve correction of certain rare immunological deficits, and it seems likely that soon we will be able to achieve correction in some of the more frequently-occurring diseases.

Let us consider this for just a moment: Patients who have the DiGeorge syndrome,[36] i.e., who are born without a thymus and completely lack the T cell population, have no demonstrable T cells in their circulating blood by any criteria. However, they do have B cells, and these comprise 85 to 97 percent of their circulating lymphocytes. Their total lymphocyte count may be normal, but their distribution of B and T cells is completely skewed and this can be recognized by examination of the peripheral blood. This abnormality can be completely corrected by transplanting into their abdominal wall a tiny wet membrane of embryonic thymus.[37] It seems incredible, yet it has been done six times these past years and has just been reconfirmed in Rome with several additional successful thymic transplants.

We now can also correct severe combined immunodeficiency disease in which both the T and B cell populations are very deficient and the functions characteristic of T cells and humoral antibodies are all lacking. Transplantation of bone marrow to these patients from a properly selected (almost always) sibling donor, matched by the HLA and MLRS loci, has enabled us and others to correct fully their immunologic systems.[38] Further, in order to enable the reconstitution to persist in the face of an immunologically-induced aregenerative pancytopenia, in one instance we performed a second bone marrow transplant from the same donor and succeeded in switching the patient's blood type to one compatible with his new lymphoid system.[39] That boy remains today with all of the cells in his bone marrow and circulating blood identifiable as derived from the female donor whose marrow corrected his deficiency. This indeed

is cellular engineering!

Cellular engineering can and will be developed much further. When a matched sibling donor is available and sufficient radiation or cyclophosphamide is given, correction of aplastic anemia is achieved approximately half of the time.[40] Improving methodology and accumulating experience in this field, presently led by Donnell Thomas, is leading to continually improving results. However, only rarely (approximately one time in ten) is a matched sibling donor available. Thus, the major problem in extending this approach to the general population is the difficulty of identifying a suitable donor to provide the basis for correction of the aplastic anemia with sufficient frequency, and I shall discuss this aspect shortly. Bone marrow transplantation, in combination with high doses of cytotoxic drugs also has been utilized to treat patients who have leukemia. Both in terminal stages and early in the course such marrow transplants can frequently induce long-term remissions.[41] Cellular engineering is thus beginning to extend to diseases which occur with greater frequency, and, of course, a major interest of the field is to be able to manipulate the more commonly occurring diseases associated with immunologic deficits. Let me review for you some of the progress that is being made along this line.

Goldstein and White in New York, and Goldstein subsequently in Houston, using a rather crude extract of thymus, developed methods which they reported could convert bone marrow cells or spleen cells to T lymphocytes.[42] However, they did not have definitive means of identifying thymic cells, and there was much concern with the adequacy of their approach. Last spring, Boyse and Komuro came into this field. Boyse had been studying and mapping the surface of lymphocytes for about 12 years. He had defined one group of markers seen on the lymphocyte surface when it is in the thymus, and another group of markers on the lymphocyte when it has graduated from the thymus to the periphery. These markers, along with other markers of stages of differentiation and isoantigenicity, could serve to define the origin, lineage, stage of development, and activity of the T cell, an extraordinary aspect of the differentiation of these cells.[24] Using a Goldstein-type extract of thymus, Boyse and Komuro were able to induce a display of the thymic-specific TL, theta and LY isoantigens on bone marrow or spleen cells within a two-hour period by a process which did not require cell division. This display had to reflect that these cells had become committed to develop into thymic cells. Further differentiation occurred in association with cell division.[43]

In collaboration with Gideon Goldstein, who began to purify his factor based on its ability to interfere with transmission at the myoneural junction,[44] Schlesinger isolated a peptide of 7,000 daltons molecular weight which he now has almost completely sequenced.[43] This substance in picogram quantities will induce the display of thymic antigens on the surface of spleen or marrow cells. Further, while putative stem cells from the marrow, spleen, or fetal liver could be so induced, cells from the yolk sac could not. This indicated that there are steps in differentiation which are required to prepare a cell to be responsive to the influence of this polypeptide. Consider a polypeptide of only 7,000 daltons —it is not only sequenceable, it is synthesizeable! Thus, this molecular analysis and biology, only in its infancy, already is concerned with molecules of a size with which the American pharmaceutical industry can deal. Such manipulation of cell surface and function by use of various macromolecules may well have important implications with respect to the treatment and correction of the underlying defects in a variety of the diseases of man.

Recently we were able to take my own bone marrow and fractionate it into a stem cell layer which would grow in soft agar to form distinct colonies of erythrocytes, eosinophiles, granulocytes, monocytes and phagocytes. When this marrow fraction containing putative stem cells, but lacking demonstrable T cells, was exposed to an extract prepared from a human thy-

mus, within two hours the appearance of T cells which formed characteristic rosettes with sheep erythrocytes was observed. We could repeatedly induce the appearance of cells which had thymus-specific antigens on their surface, similar to the thymic lymphocyte antigens previously described,[24] and thus can apply the incisive mouse systems in trying to develop approaches to the crucial problems of human immunobiology. We know already that the athymic patient has cells that can be readily differentiated but the patient with severe combined immunodeficiency lacks cells that will respond to this differentiative influence or inducer. Thus this new approach permits us to dissect in a new way the primary immunodeficiency diseases.

We have focused on certain rare diseases not only because they concern us as primary problems, although of course each individual who has such a disease is important, but also because they reveal such basic processes and insights which are applicable to the biology and health of the population at large. For example, study of selective absence of IgA, which occurs in approximately one of 700 individuals depending upon the geographic area under consideration, has shown remarkable association of this condition with autoimmune disease.[45] This realization has helped us learn an extraordinary lesson: the occurrence of immunological excesses as reflected in autoimmune processes is almost always associated with an immunologic deficiency, which is lurking in the background and permitting or inducing the excessive stimulation to occur. Even allergy is probably related to an early developmental defect of the IgA system, such that when you cannot say "A," you are likely to say "E."[46]

We now see immunodeficiencies so regularly that we can begin to associate certain abnormalities with given types of infections. Von Pirquet,[47] around the turn of the century, taught us that measles could be associated with a temporary anergy. Smithwick, now with us at the Sloan-Kettering Institute, was able to show *in vitro* that infection with the measles virus could render lymphocytes unable to respond in a mixed leukocyte culture or to phytohemagglutinin,[48] thus defining the basis for the anergy seen by von Pirquet. Olson, Dent, Rawls, *et al.*[49] confirmed these findings and extended them to several additional viruses. Thus, viruses are not so dumb—they can influence the system that resists them and favor successful infection by inducing an immune deficiency. Exactly how they do this is not yet clear.

Immune deficiencies occur in non-viral infections also, *e.g.*, lepromatous leprosy in which an inversion of the proportions of circulating T and B cells is seen.[50] Immune deficiency occurs with aging: Makinodan showed deficits of both T and B lymphocyte function with aging,[51] and we showed an association of aging, immunodeficiency, autoimmunity and malignancy in the experimental animal.[52] One also sees profound perturbations of the immunologic system in nutritional disturbances; these are being analyzed and quantified with the newer methodologies.

However, one of the most fascinating associations is that between immunodeficiency and cancer. We became interested in this relationship because we were studying the lessons of the experiments of nature in patients with primary immunodeficiency disease. Patients with X-linked infantile Bruton-type agammaglobulinemia, who as far as we could discern, had an intact or even hyperactive T-cell system were developing malignancy with an incidence of 10 percent, as compared to an incidence of 0.007 percent among children in the general population. Further, the malignancy that they developed often appeared in the thymus and was a leukemia.[53]

Patients with ataxia telangiectasia also developed cancer too frequently. Autopsy examination showed that 35 percent of these young people had a tumor—an extraordinary 1,000 to 10,000-fold increase over the incidence of malignancy in the childhood population generally. The malignancies usually occurred in the lympho-

reticular system and occasionally in the gastrointestinal tract, but a variety of other cancers also were seen.[53]

Patients with the common variable form of immunodeficiency disease are most interesting in this regard. These patients lack plasma cells, yet have cells that synthesize but do not secrete immunoglobulin; they often have T-cell deficits as well.[54] They also develop neoplasms, especially of the stomach and the colon, far too frequently. They also frequently develop pernicious anemia, with achlorhydria, early in the course of the disease. Their pernicious anemia occurs about 30 years earlier than it does in the general population.[55] Could it be that their immunodeficiency disease is a consequence of an abnormality of their gastrointestinal tract that ultimately plays out as achlorhydria, pernicious anemia, and/or malignancy?

A relationship with malignancy also is seen among the iatrogenically-induced immunodeficiencies. Cancer has sometimes inadvertently been transplanted along with a renal graft, and become disseminated widely throughout the body. Further, in a few instances, it has been completely eliminated simply by stopping the immunosuppressive therapy required to keep the kidney transplant in place, (presumably) allowing the immune system to eliminate the tumor.[53]

However, the most important association between cancer and immunodeficiency that I see is the peculiar ability of a cancer to somehow or other produce an immunodeficiency. We see this particularly in cancers of the head and neck, breast, and colon, and, to a lesser extent, in other widely disseminated cancers. As the cancer advances, we see the immunodeficiency developing by evaluation of the immune apparatus and its responses. We can see this earliest by histopathological evaluation of the regional lymph nodes, and even can plot the prognosis of patients with cancer by simply evaluating these regional lymph nodes in modern immunobiologic terms. A pattern associated predominantly with expansion of the T cell population is associated with a relatively good prognosis; surprisingly, a B cell or germinal center-predominant pattern is associated with a somewhat less favorable prognosis; while a lymphocyte-depleted pattern is associated with a poor prognosis. Now, what is the cancer doing to deplete that lymphocyte population?

One of the clearest reflections to me of the interrelationship between cancer and immunity is the realization that the best immunofacilitation therapy we have thus far found is the effective treatment or elimination of the cancer itself. If a tumor is removed by surgery, radiation or chemotherapy, the immune response frequently will come bouncing back like a rubber ball. What is this special relationship? Deaths from cancer are, by and large, not deaths from cancer *per se;* they are deaths from infection. If the only therapeutic achievement which derives from understanding and manipulating the immunological system relevant to cancer would be to correct the extraordinary susceptibility that many of these patients display to a variety of opportunistic infections, we would have done all that really ought to be required of immunotherapy.

However, I think it is already very clear that it is possible to combat the cancer itself with immunological methods. Drs. Pinsky and Oettgen in our Center are treating skin melanomas very effectively by local injection of BCG. They have an observation that must be analyzed and understood, in that in some instances other melanomas in these same patients resolved simultaneously, and rarely a concomitant resolution of associated melanoma also was seen. More recently, Rudy Falk occasionally achieved disappearance of the skin melanoma in men by simply feeding BCG. In other quarters, Curry seems to have increased the effect of BCG by combining its administration with immunization with inactivated melanoma cells. There is much to learn about the mechanisms underlying successful therapy with BCG.

There seem to be extraordinary possibilities for the molecular manipulation of

cancer, as well as for the manipulation of malignant disease by cellular engineering as discussed above. Larry Helson, a pediatrician at the Memorial Sloan-Kettering Cancer Center, has been able to cause neuroblastoma cells to differentiate in culture. When he treats these cells with a phosphodiesterase inhibitor which they take into their cytoplasm, these wildly malignant cells differentiate to seemingly benign ganglioneuroma cells! Could such cells make a vaccine appropriate to be utilized in the neuroblastoma patient? Helson has performed similar experiments with malignant melanoma cells. Both instances seem to involve the "third biologic language," represented here by surface-to-nuclear signals which seem to control the alternative cell responses of (a) performing the functions of a differentiated cell, on the one hand, or (b) proliferating to malignancy, on the other.

I would like to close by telling you a really exciting story about histocompatibility control, and reviewing the present state of this field, because I think that it is a tool which we are going to find ourselves using in every branch of medicine. The mouse has a chromosome containing the H-2 region, which controls the major histocompatibility antigens. At one end of this region is the H2D locus, a polyallelic system of about 20 alleles, and at the other end is the H2K polyallelic system, again with 20 or more alleles. The real credit for defining this locus belongs to Snell and Gorer and their students.[56] One also finds in this linkage group the Ss-Slp system.[57] Here also is a fascinating marker: IR-1 locus that has been defined by Benacerraf and McDevitt in independent investigations.[58] What is this latter locus? It is a polyallelic system that determines whether or not the T cell immunity system can respond to particular antigens.

During the period that these concepts were being developed in the mouse, a comparable region of a chromosome in man, termed HLA, was being studied. This was first detected by Dausset who discovered Mac, an antigen that could be defined by an antibody which agglutinated lymphocytes and revealed what now is known as the LA locus of this system.[59] It has at least 16 alleles, of which 13 are well established. There is another closely linked histocompatibility locus in man, called FOUR, which like H2K, may have at least 20 alleles.[60]

In our first successful transplant of bone marrow, we not only had a mismatch at the ABO locus (the donor was type O while the recipient child was type A); the donor and recipient also were mismatched at the LA locus. However, they were matched with respect to both the FOUR locus and the mixed leukocyte culture assay, and upon transplantation, a fatal graft-versus-host reaction was not seen. This attracted our attention to the possibility that the LA locus could be completely dissociated from the mixed leukocyte culture reaction, but we did not really understand this until Edmond Yunis studied a large Minnesota family.

In this family were two pairs of siblings who were matched at the HLA loci. If the mixed leukocyte culture reaction, lymphocytes of one pair should stimulate lymphocytes of the other pair but not each other. HLA system really was responsible for the Yet, the cells of one member of the first HLA matched pair of siblings stimulated cells of the other member of this HLA matched pair as well as the cells of both members of the other HLA matched pair. The cells of the other member of the first HLA matched pair didn't stimulate either member of the second matched sibling pair even though they were completely different by HLA typing. This showed that the locus which controlled the mixed leukocyte culture reaction had to be separate from the HLA system. Subsequently, a number of families studied at Duke and Minnesota, by Amos and Yunis,[61] and additional cases which we have studied with Bo Dupont and Yunis, have clearly established that the control of the mixed leukocyte culture reaction can be separated from HLA.[62]

A number of parallel developments supported this conclusion. One was the observation that whereas renal transplants

between siblings matched at the HLA locus showed a five-year survival of 97 percent, perfect HLA matches in the general population resulted in at most a 50 to 70 percent five-year survival. This represented very little gain over the survival of renal grafts between non-HLA matched donors, and intensive immunosuppression had to be used to achieve even this success.[63] This was discouraging until the underlying basis was understood.

Then, approximately two years ago, I was asked to go to Copenhagen to consider an interesting situation. A pathologist's child had severe combined immunodeficiency disease, lacking both the B and T cell immunity systems. There were no siblings, and of course a marrow transplant mismatched at a major locus could lead to the death of the child via a graft-versus-host reaction. The HLA system and the mixed leukocyte culture reaction had been analyzed, and two uncles who matched with each other, the mother and the patient, at what we now call the MLRS locus, were found. However, both uncles were double haplotype mismatches with the recipient at both the FOUR and LA loci. The question was whether to transplant. Would this induce a graft-versus-host reaction? I suggested proceeding because the child had no alternative. Further, this also could establish whether or not the MLRS locus was a major determinant of histocompatibility linked with the graft-versus-host reaction, and thereby could provide a critical insight in the effort to restore the children with this disease to normal health. This child was treated with his uncle's marrow, which fully corrected his immunologic system without inducing the fatal graft-versus-host reaction. He now is in good health.[63]

We have just carried this one step further. We have recently been able to correct in New York the severe combined immunodeficiency disease of a child born in Ohio, by transportation and transplantation of bone marrow from an unrelated donor in Copenhagen, again despite mismatches at the LA locus. Once more, concern for and study of the patients with these rare diseases has pointed out a fascinating and generally applicable biological principle. Bo Dupont with us in Minneapolis was able to work out the details with Edmond Yunis in the context of a new histocompatibility locus termed "MLRS," which has now been analyzed genetically and shown to segregate independently of and to be quite separate from the LA and the FOUR loci.[62]

In the course of these investigations, an attempt was made to use transfer factor, that strange molecule of 2,000 to 4,000 daltons with which Jerry Lawrence has been working for the last 20 years[64] in an effort to correct the immune deficiency of a child with the Wiscott-Aldrich syndrome. This patient was matched with his mother at the MLRS locus, a condition which can obtain if the father and mother share a haplotype. Upon treatment with transfer factor, the lymphocytes of the child and the mother began to respond to each other. Here, transfer factor seemed to have altered the responsiveness of the recipient lymphocytes to antigens against which the donor could not have been responsive. We also saw in other patients with the Wiscott-Aldrich syndrome evidence that the influence of transfer factor could be nonspecific. In several instances administration of transfer factor prepared from donors not previously stimulated with 2,4-dinitro-chlorobenzene (DNCB) could impart cellular immunity to this agent to previously nonreactive recipients, who had been challenged with subthreshold amounts of DNCB during the course of therapy. Thus, it now seems possible that transfer factor imparts a nonspecific rather than a specific influence, and that the specificity is imposed, not by the transfer factor *per se*, but rather by minute amounts of antigen which are presented to the immune system along with the transfer factor. However, this is a controversial area which still requires much clarification. These same observations led Dupont, Yunis and I to conclude further that there existed a separate genetic locus between FOUR and LA and separate from the strong MLRS locus that Yunis had

located outside the HLA system. The cell responses controlled by this locus, we believe, are the ones we have manipulated with transfer factor.

A number of diseases now have been linked to the FOUR locus in the HLA system. In ankylosing spondylitis and Reiter's syndrome, greater than 90 percent of afflicted individuals have the W 27 allele at the HLA locus.[65] Celiac disease and systemic lupus erythematosus seem to show a weak linkage to the FOUR locus.[66] Multiple sclerosis is fascinating in this respect. Of the 20 or so known alleles at the FOUR locus, one allele is present about two times more frequently than it occurs in the general population.[66]

Now, when Bo Dupont returned to Copenhagen, he joined his friend, Jersild, who was working on the association of various diseases with the histocompatibility loci. They began to analyze the MLRS locus by a neat trick which involved use of lymphocytes of intermarried cousins and their offspring. Those lymphocytes which failed to stimulate the lymphocytes of either parent were used as reagents, and with this methodology, they were able to identify at least 10 alleles which operate at the MLRS locus.[67] They found that one of these, which they have termed the "7" allele, was seen in almost all patients who had multiple sclerosis of the rapidly progressing type, but less frequently when the multiple sclerosis was of the slowly progressing type.[68] This suggests that there are two kinds of multiple sclerosis, and one kind seems to require a characteristic which is genetically determined via the MLRS histocompatibility region. Subsequently, Dupont and Jersild found that transfer factor administered to the patients with rapidly progressive multiple sclerosis rendered them capable of responding to allogenic cells of the 7A allele, apparently not by altering the genetic constitution of the recipient lymphocytes, but rather by making them capable of responding to the antigens of otherwise minor "subliminal" genetically-determined histocompatibility loci.

John Adams, one of my professors of pediatrics at the University of Minnesota, had long ago linked multiple sclerosis firstly to the distemper virus that produced a demyelinating disease in dogs, and, secondly, to the measles virus which is closely related to this distemper virus.[69] Further, antibodies against measles virus have been seen very frequently in the spinal fluid of patients with multiple sclerosis, and high titers of circulating antibodies to the measles, mumps, and paramyxo-three viruses occur far too frequently in patients with multiple sclerosis as compared to the general population to be explained by chance alone.[70] Clearly, the patients with rapidly progressive multiple sclerosis have been exposed to these viral agents. However, neither Dupont and Jerslid, nor Zabriskie at the Rockefeller University who approached this problem from a different perspective,[71] were able to find cellular immunity to these viruses in many of these patients, even using the newest and most sensitive methodologies. In short, this seemed to represent another "lacunar immunodeficiency," with cellular immunity selectively lacking to certain microorganisms only. Further, this deficiency was a consequence of a genetic constitution derived from a given MLRS allele, which thereby linked the rapidly progressive form of multiple sclerosis to a certain group of viruses against which a fully normal immune response could not be made. This predisposition to certain infections at last is beginning to be therapeutically manipulable In work almost too preliminary to discuss properly, repeated administration of transfer factor seemed not only to enable these patients with multiple sclerosis to marshal a cellular immune response to the measles virus, but also to limit the progressiveness of this otherwise rapidly rampant form of multiple sclerosis. What a very exciting new approach!

Thus, the entire major histocompatibility region is a powerful instrument now under intensive investigation. Already we can define the LA locus in 95 percent of individuals, and can define the FOUR locus similarly well; in a few years we also

will have defined the alleles of the MLRS locus. We soon will be able to look at the entirety of this new instrument—the major histocompatibility region and its biology—to yield incisive new techniques for diagnosing, interpreting and manipulating the diseases of man. Certain diseases undoubtedly occur because one has a genetic constitution which renders him susceptible. This may explain critical steps in the pathogenesis, and suggest approaches to prevention or treatment, of diseases like paralytic polio, progressive active hepatitis, and even certain kinds of malignancy in which only a few among the many of us exposed ultimately are affected. It is becoming increasingly critical to consider these genetic factors in the ultimate design of prophylactic and therapeutic agents.

In summary, a combination of macromolecular and cellular engineering, ultimately extending to and manipulated via micromolecular engineering or small molecule pharmacology, may well become the new way of approaching innumerable diseases. Whereas we began with a concern largely for the rare diseases, we now are looking at the common diseases of man in a completely new and incisive way. This entire field is only in its infancy. We must and will develop these immunologic approaches, and continue to develop more suitable and critical means of extending them for the benefit of mankind. Surely the thought processes of modern immunobiology will continue to be at the center of the medicine of the future, and surely also, your Department of Immunology which we are celebrating today, will be among those which is leading the way.

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IMMUNODEFICIENCY: A CELLULAR AND MOLECULAR APPROACH

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ABSTRACT. The differentiation steps in the development of B lymphocytes, and the assembly and secretion steps which follow antigenic stimulation, are rapidly being defined. Immunodeficiency diseases can now be related to given faults of differentiation, or to specific biosynthetic abnormalities. This knowledge promises to offer new therapeutic approaches to immunodeficiency states in the near future.

The original observations of the immunodeficiency syndromes prompted inquiry into the mechanisms by which normal immunity is obtained. Combining animal experiments with the study of clinical syndromes has yielded understanding of the mechanisms by which the characteristic broad range of responsivity of the immune system is obtained. Recent *in vivo* studies provide insight into the assembly and secretion of the polypeptide products which are the effectors of humoral immunity. Presently described immunodeficiency syndromes can be considered as errors in these normal pathways. Study of the scheme also permits prediction of future disease courses.

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THE DIFFERENTIATION STEPS

Fig. 1 is a concept of the development of the clones which will ultimately produce the immunoglobulins in mature adults based largely on the work of Cooper[1] and Paul.[2] The stem cell, as depicted in the figure, has the capability of becoming a T-cell and perhaps also a cell of the hematopoietic system; however, only the B-cell differentiation pathway is shown here. One essential feature of this scheme is that the original precursors of the B lymphocyte system probably all bear receptors of the mu class. Recent work has shown that delta receptors are also present on the mu cell, but whether this is a late acquisition or whether the primordial B-μ lymphocytes also carry delta receptors is at present unknown. Experiments in the chicken, mouse, and guinea pig indicate that the earliest lymphocytes detectable all bear mu receptors. By a series of steps which are antigen-independent in the chicken and which probably take place in the bursa of Fabricus, mu bearing lymphocytes differentiate into gamma chain-bearing lymphocytes. It is possible that gamma lymphocytes then, in turn, become alpha lymphocytes, although the general

occurrence among all species of this event is unknown. Steps leading to delta and epsilon lymphocytes are at present undefined. In the mouse, however, the process of differentiation is probably antigen-driven, and in the guinea pig there seems to be evidence that development of B-alpha lymphocytes precedes the development of B-gamma lymphocytes.[3,4] In any event, development of B lymphocyte surface receptors appears quite early as an intrauterine event, and by 13 weeks in humans, the normal numbers of lymphocytes of three major classes are already found.[5] At this time there are no secreted immunoglobulins detectable in fetal serum. The relative isolation in the fetus from antigenic exposure suggests that these developmental steps are relatively antigen-independent. The receipt of antigen into the environment of the human is responsible for the expansion of each of the clones and a gradual enlargement of the lymphoid cell mass in the body. On rare occasions this may occur *in utero*, in which case a marked IgM response is seen. After sufficient stimulation, the individual will have acquired the capability of producing several thousand distinct antibodies of at least five major classes.

THE ASSEMBLY AND SECRETION STEPS

The initiating event calling for the secretion of immunoglobulin is a stimulation of the B lymphocyte by an antigen. It has been suggested that the initiation of Ig production will not occur, however, unless a second signal occurs.[6] As shown in Fig. 2, a number of substances can produce this second signal *in vitro*. Under certain

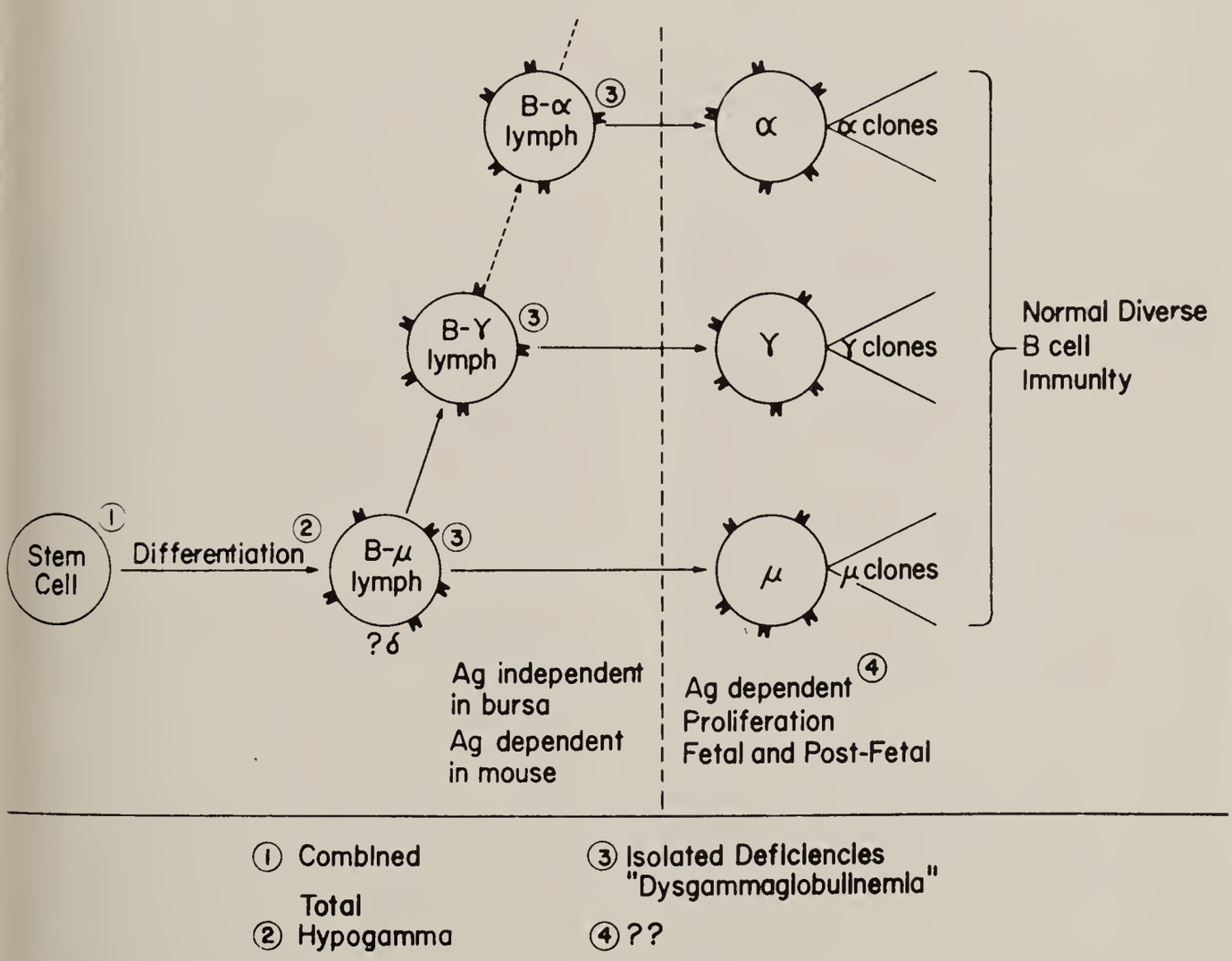

Fig. 1—Differentiation of B-lymphocytes (Ref. 1). See text for explanation. Numbers refer to postulated sites involved in diseases of immunodeficiency.

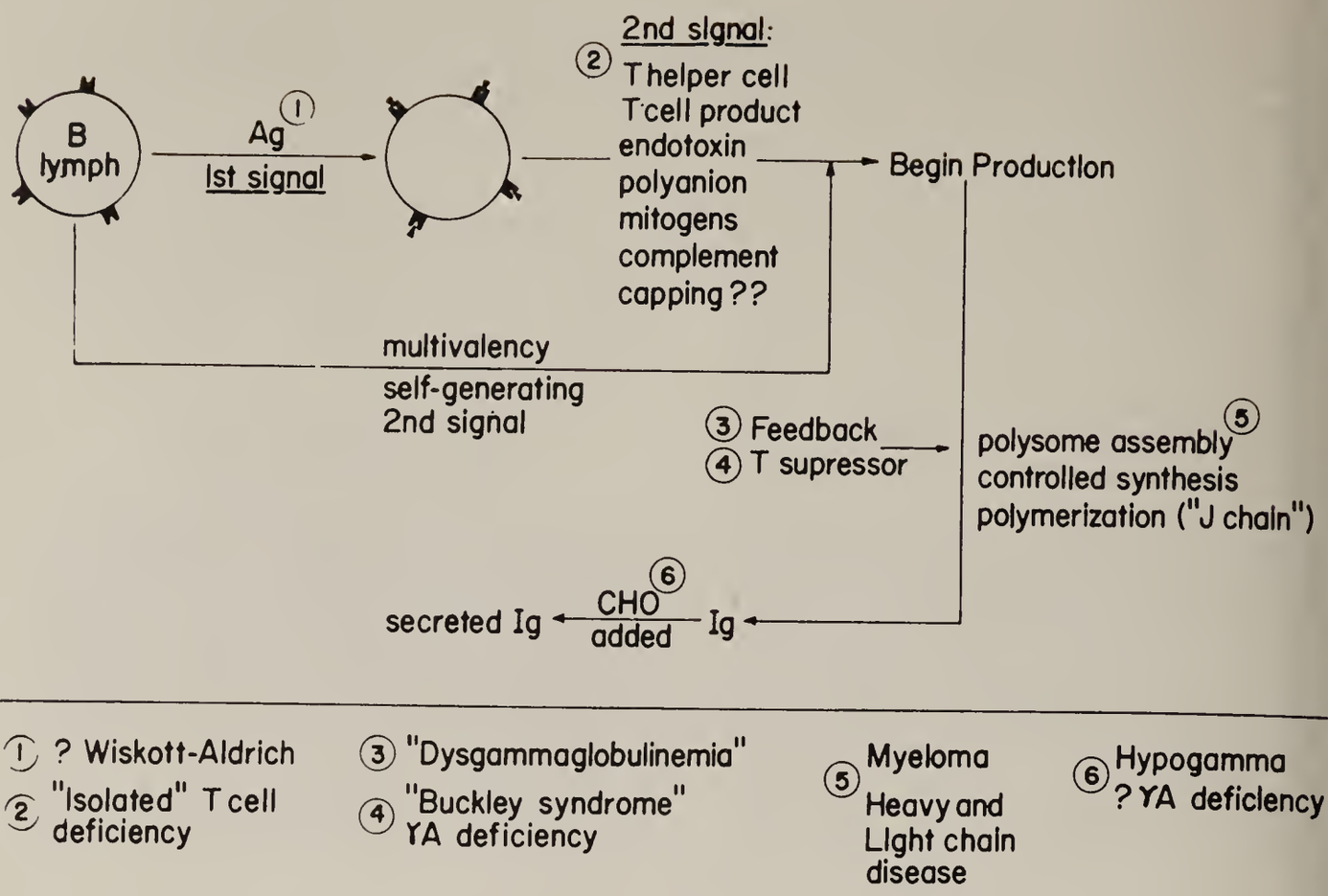

Fig. 2—Assembly and secretion of immunoglobulins. See text for explanation. Numbers refer to postulated sites involved in diseases of immunodeficiency.

circumstances the character of the antigen (having a repeating sub-unit structure) is sufficient to bypass the necessity of the second signal. Such an antigen may be considered thymic, or second signal-independent. After the cellular machinery begins to respond to the external events which call for the initiation of immunoglobulin production, the polypeptide chains are assembled on their separate ribosomes. For two of the immunoglobulins (IgA and IgM) a polymerization step is also necessary and this requires another polypeptide known as "J" or "joining chain."[7,8] The immunoglobulin, however, cannot leave the cytoplasm simply at will, for the secretory process is regulated. Some evidence indicates that the addition of carbohydrate is a prerequisite which permits the completed immunoglobulin molecule to be secreted to the exterior.[9]

Homeostasis and control of the immunoglobulin production scheme is accomplished by a normal negative feedback mechanism in which the elaboration of specific antibody tends to suppress its further synthesis; IgG antibody normally suppresses IgM synthesis.[10] Recent evidence also indicates that a subpopulation of T-cells known as "T suppressor cells" also has the capability of controlling immunoglobulin response."[11]

DEFICIENCY STATES

Fault in either differentiation or the intracellular steps just described can be envisioned as fundamental causes of immunodeficiency syndromes. Examples are indicated by the numbers in the figures. Thus, a fault of the stem cell will result in combined B and T cell immunodeficiency syndromes. Failure of development of the B lymphocyte at the next stage can result in total hypogammaglobulinemia of all the major classes. Inability to generate one particular class of B lymphocytes can result in isolated deficiencies of one or more of the immunoglobulin classes, or so

called "dysgammaglobulinemias." The possibility of inappropriate or weak expansion of the individual clones as a result of poor response to antigen is at present unknown but can be predicted as a possible event.

Concerning the surface and intracellular events, it can be seen that inability to respond to a given antigen can result in lack of initiation of the immunoglobulin production steps. The inability of patients with Wiskott-Aldrich syndrome to respond to carbohydrate antigen would be an example of such a disorder. Patients with isolated T-cell deficiency would have some impairment of their B-cell product production, but insofar as antigens can bypass the necessity for T helper cells or other agents as shown can effect a second signal, the degree of B-cell deficiency secondary to isolated T-cell problem is extremely variable. In some syndromes marked elevation of immunoglobulins is observed and one could postulate a fault in the feedback mechanism. Recently, Buckley[12] has described a syndrome in which markedly high levels of IgE are found in association with chronic cutaneous infections. Although there is no proof for the clinical significance of T suppressor populations in control of human disease, in rats T-cells clearly affect IgE synthesis. Thus, markedly elevated γE levels may be a sign of T suppressor lack in man. In selective γA deficiency it is now appreciated that there can be the association of subtle T-cell abnormalities; some patients show marked elevations of IgE.[13]

Disruption of the internal synthetic machinery is present in the malignant disorders known as myeloma and the variants, heavy or light chain disease.

Finally, it has been shown that some patients with hypogammaglobulinemia seem to have normal numbers of B lymphocytes, and under certain *in vitro* situations, these cells can be induced to increase their quantity of intracellular globulin. Experiments by Choi[14] imply that the addition of carbohydrates is impaired in these patients and it may be that one of their major defects is one of secretion.

CLINICAL STUDIES

A number of clinical studies provides support for the foregoing. If one examines the immunoglobulins which are produced by patients with hypogammaglobulinemia, one finds that they are not normal. Thus, the basic defects in hypogammaglobulinemia are not simply a restriction of the numbers of cells which are capable of producing immunoglobulins nor is it simply a decrease in numbers of molecules which ultimately are released from the cell. Table I shows abnormalities which can be found in immunoglobulin populations isolated from patients with hypogammaglobulinemia when studied by antigenic or chemical means. These data show that the molecules are functionally less adequate than those of a normal heterogeneous population of gamma globulin molecules elaborated by normal individuals.[15,16]

Furthermore, there is suggestion that there is a perturbation of intracellular synthesis. The resemblence between abnormalities revealed in these studies is amazingly similar to those which are seen in

TABLE I

ABNORMALITIES OF IG'S IN HYPOGAMMAGLOBULINEMIA

Reversed kappa/lambda ratios
Unusual IgG sub-class distribution
Limited heterogeneity
Deficient complement fixation
Imbalance of sub-unit synthesis (excess 7S IgM, light chains)

myeloma in which a malignant process deranges intracellular machinery. Of interest in this regard is the observation that one form of myeloma, light-chain disease, is usually associated with hypogammaglobulinemia rather than hypergammaglobulinemia. In this condition it is thought that the synthesis of heavy chain is somehow suppressed, and the light chains are released into the circulation without any heavy chain attached. Parallel with this observation is the demonstration of unusual amounts of free light chains in the serums of patients with the congenital disorder, hypogammaglobulinemia.[17]

The above studies indicate that the actual synthetic mechanisms in hypogammaglobulinemic disorders are deranged and that the fault is not simply one of faulty differentiation leading to a low number of immunoglobulin secreting units.

FUTURE PROJECTIONS

The ultimate goal in understanding immune disorders is to provide rational future therapeutic approaches. Understanding of the mechanisms by which the ultimate goal of immunoglobulin of known specificity is secreted and the ability to define a particular fault to a deficiency state should allow a mechanism for useful intervention in the future. Recent reports showing the responses of B and T lymphocytes to various agents *in vitro* suggests that defective cell populations may be corrected *in vitro*.[18–20] Hopefully, in the future they can be returned to the host to remedy the defect.

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IONIZING RADIATION AND THE STEM CELL-MEGAKARYOCYTE-PLATELET SYSTEM: A MODEL CELL RENEWAL SYSTEM

ALEXANDER NAKEFF

There are a number of areas in cell biology that are of great interest to both the basic researcher and the radiation oncologist and where advances can be rapid and have a profound impact on both groups if pursued cooperatively. Among such areas can be included the following: cellular kinetics of solid tumors and the assay of important subpopulations, such as clonogenic and anoxic cells; dose fractionation for various types of tumors using specific data on both the tumor population and that of the supporting normal tissue; late effects of normal tissues as they reflect a compromised microcirculation and particularly the effects of ionizing radiation on the proliferative activity of endothelial cells; and the rational use of the combined modalities of radiation and chemotherapy so as to maximize destruction of malignant cells while minimizing killing of normal, rapidly-renewing cell systems such as the gastrointestinal epithelium and the hematopoietic system.

The following discussion on the effects of ionizing radiation on the stem cell-megakaryocyte-platelet system has particular reference to the last named area. Platelets are formed elements circulating in the peripheral blood, which are not only essential in the initiation and maintenance of hemostasis but also important in maintaining the cellular integrity of the blood vasculature. Compromising the steady supply of new platelets leads inevitably to gross, and frequently lethal, hemorrhage. Thus, damage to this vital cell-renewal system by radiation or drugs, or both, is an important factor limiting the aggressiveness of therapeutic measures designed to eradicate malignant growth. Knowledge gained about the kinetics of this cell population and its response to various cancer therapies, therefore, should permit a more rational design of treatment schedules. In a more general context, techniques and concepts arising from fundamental studies of normal cell kinetics can easily be applied (and have been applied) to tumor cell systems. An example is the evolution of the G_0 compartment concept from defining the kinetics and physiology of the hematopoietic stem cell to a population important in the definition of growth fraction in tumors and finally to the basis for specific drug combinations in treating solid tumors. Further, the present concept of considering cancer to be primarily a manifestation of a loss of feedback control, either humoral- or cell-mediated, could be tested rationally once the normal control mechanisms and their actions were known.

The stem cell-megakaryocyte-platelet system is defined in Fig. 1. Platelets circulate in the peripheral blood and are derived from megakaryocytes whose sole function it is to form platelets as enucleate fragments of their cytoplasm. Megakaryocytes, in turn, are derived through differentiation of hematopoietic stem cells. The stem cell compartment is thought to comprise two subpopulations, one composed of pluripotential stem cells capable of differentiation into the erythyroid, myeloid, lymphoid and megakaryocytoid cell lines, and the other subpopulation composed of cells committed solely to a given cell line such as the committed stem cells of the

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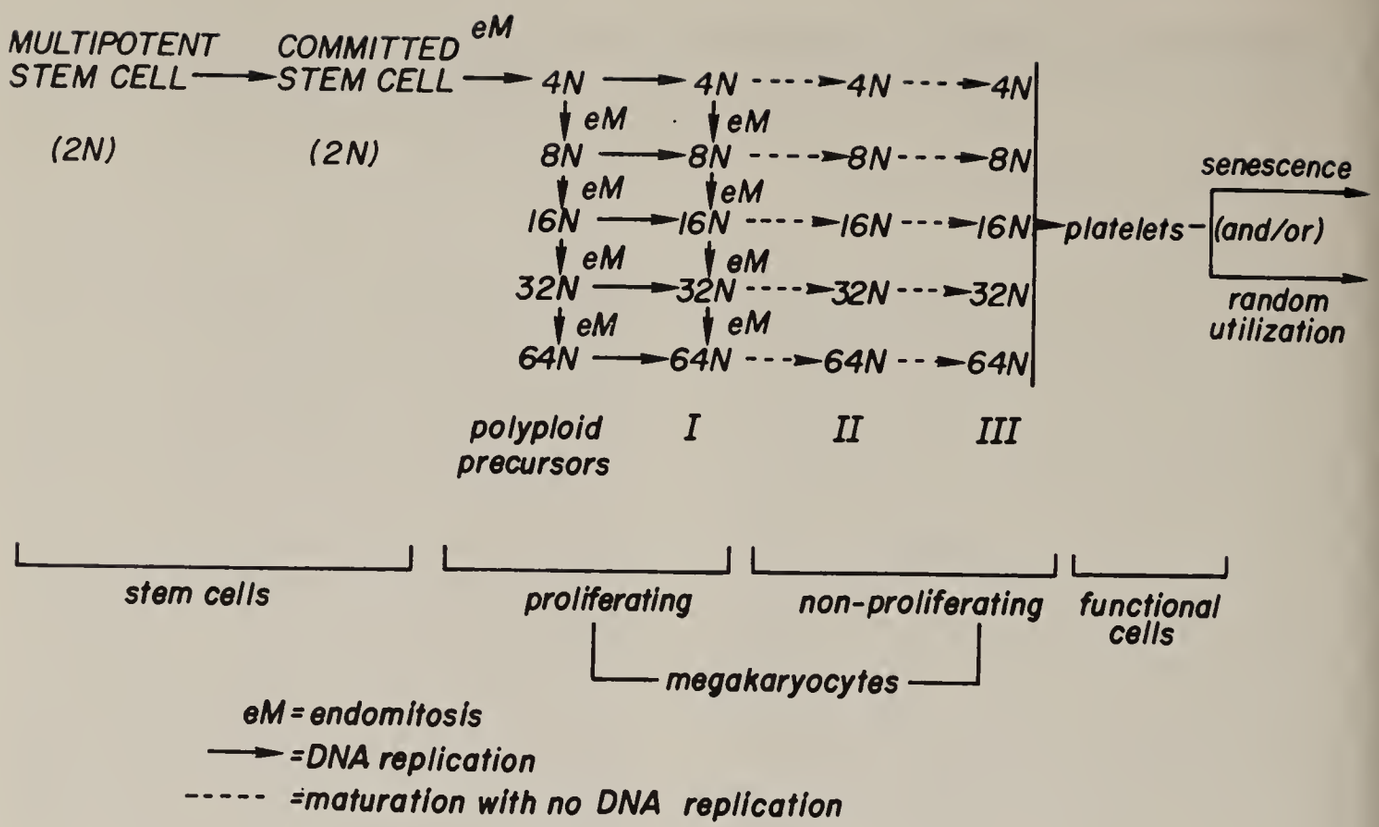

Fig. 1—A model of megakaryocyte and platelet production. I, II and III indicate morphologically-identified stages of increasing cytoplasmic maturation. The multipotent and committed stem cells plus possible polyploid precursors remain morphologically unidentified with their existence being supported by functional and cell kinetic data.[1]

megakaryocytoid cell line.[1] The latter may be polyploid in distinction to the pluripotent stem cell which is thought to be diploid. The committed cell compartment is hypothetical at this stage but recent data[2] in rats tends to confirm its existence. All of the proliferation necessary to attain ploidy values as high as 64N (approximately five nuclear divisions without concomitant division of cytoplasm) occurs in a stage of development that cannot be identified morphologically. That is, megakaryocytes that comprise the morphologically-identified compartment are no longer capable of cellular proliferation, as confirmed by tritiated thymidine labeling studies. Thus, megakaryocytes that can be identified morphologically are in the process of cytoplasmic maturation. The transit time for a megakaryocyte to go from its most immature state to its functional state, the platelet, has been measured in the rodent to be about 2.5 days. When the megakaryocytes reach complete cytoplasmic maturity, they are each capable of producing about 5,000 blood platelets from their cytoplasm. Once the newly-produced platelets enter the peripheral blood, they are either utilized in the maintenance of vascular integrity or die through senescence with a half-life of about 1.5 days.

Let us consider this system as a model for studying the effects of ionizing radiation on a cell-renewal population. While it is generally believed that the radiosensitivity of such a population is directly proportional to its mitotic activity and inversely proportional to the extent of its differentiation, the radiosensitivity more likely reflects the relatively small fraction of this population consisting of stem cells. Doses of a few hundred rads can reduce the surviving fraction of the stem cells to levels of 10 percent or so, and subsequent 200 to 300 rad increments further decrease the surviving fraction by factors of 10. The surviving fraction is assayed in terms of the stem cells' ability to undergo extensive proliferation. For cellular functions such as protein synthesis or enzymatic activity, extremely large doses of radiation are required for their significant modifica-

tion. Because of this, low doses of radiation (in the order of hundreds of rads) would be expected to affect significantly the proliferative state of a cell population but have little direct effect on its functional state.

One useful theoretical approach to the effect of radiation on such a cell system is to compartmentalize those cells that are morphologically or functionally distinguishable as is presented for the stem cell-megakaryocyte-platelet system in Fig. 2. In considering a compartment in which cells might reside, three kinetic parameters can be used to define possible cell movements; these are input, output and proliferation. In this manner, eight different combinations (or compartments) can be defined, of which two are of major importance here; they are the stem cell and transit cell compartments.

The stem cell compartment is characterized by 1) having no cell input, 2) being self-maintaining, that is, proliferation occurs within the compartment, 3) supplying cells as output which either are, or give rise to, differentiated cells; and 4) responding to regulation (either cell-to-cell or humoral). Two types of stem cell compartments can be defined, one in which all cells in the population are proliferating with a 50 percent death rate in the steady state and another having only a proportion of the cells actively proliferating; those cells that are not proliferating are considered to be in a resting or G_0 state. This latter type of stem cell population is found not only in bone marrow but also in liver and skin and is an important component in what is referred to as a conditional cell-renewal system; since, while there may be little normal cellular proliferation, resting cells can be induced into the proliferative state to compensate for any cell loss in the population. One of the interesting aspects of this compartment is the response of these cells to modifiers of cell growth and differentia-

M_p = MEGAKARYOCYTE PRECURSOR

M_c = MEGAKARYOCYTE

P = BLOOD PLATELET

Fig. 2—Various types of compartments in the stem cell-megakaryocyte-platelet model. Arrows within a compartment indicate cell proliferation and dashed lines indicate possible sites of action of humoral feedback controls.

tion. Because proliferation can be turned on and off to provide for differentiated cells, a control point(s) is provided through which cell population size can be regulated. It is likely that a number of hormones act by regulating cell division at the level of this compartment.

A transit compartment has an input and output and, as the name implies, is a trasitional phase between two other compartments. Fig. 2 illustrates three types of transit compartments. Transit through a compartment may accomplish one of four functions: 1) It can act as a cellular amplifier with one or more cell divisions occurring in the compartment during cell transit, as in the case of a polyploid precursor (Mp); 2) It can represent a waiting stage in which a cell population exists until some demand is placed on it for functional end-cells; possibly, some G_0 cells could be placed in this category and might define one ploidy class of megakaryocytes in Mp; 3) It can represent a maturing stage in the life history of the population in which there is no proliferation, as in the case of the megakaryocyte (M_C) where cytoplasmic maturation proceeds with no concomitant cell division; 4) It can represent functional cells in which cell loss is the result of cell death or utilization, as exemplified by the platelet population (P).

We can now attempt to predict the effects of different doses of ionizing radiation on these cell populations; first consider a stem cell population exposed to low, moderate, or high doses of radiation.

Following a small dose of radiation as shown by I in Fig. 3A, we would expect an immediate killing of a fraction of the stem cells, following which the remaining cells proliferate to repopulate the cell compartment. Some oscillation about the normal value might be expected as the mechanisms which control the cellularity of the compartment act to slow down proliferation and "fine-tune" the population size. With a larger dose of radiation, a greater initial stem cell kill would occur necessitating a longer interval of time before the compartment returned to its normal cellularity (II, Fig. 3A). Finally, a large enough dose can be administered so as to destroy all the stem cells in which case repopulation could then obviously not take place (III, Fig. 3A).

In mice which have received various doses of radiation, the number of hematopoietic stem cells (CFU-S), as measured by the spleen-colony assay, follow these predictions as shown in Fig. 3B.

Following 300 rads of gamma-radiation, there is an initial rapid killing of approximately 90 percent of the CFU-S. Over the next 24 to 48 hours, there is a further decline in the number of CFU-S, probably through some differentiation of the surviving CFU-S. Repopulation of the marrow by the remaining CFU-S is complete within about 15 days. Increasing the total dose to 500 rads results in a more marked depletion of this population which nevertheless is able to recover to its preirradiation level, although in a longer period of time. The administration of doses in the order of 800 rads (not shown) results in the killing of CFU-S to undetectable levels from which recovery is so delayed as to be unable to prevent the recipients' death. Thus, following 300 or 500 rads of whole-body irradiation, mice are able to repopulate their stem cell population and so survive the irradiation. It is well known that following approximately 800 rads, mice succumb to what is described as "hematopoietic death." These findings are applicable not only to the effects of radiation but also to a chemotherapeutic agent such as cyclophosphamide[3] which is also cytotoxic to stem cells.

What would be the response of a differentiated cell compartment following different doses of radiation? As indicated in Fig. 4A, the solid lines represent our previous predictions in Fig. 3A for the cellular response of the stem cell compartment to three different doses of radiation, and the dotted lines indicate possible corresponding changes that one might expect to observe in the differentiated (megakaryocyte) cell compartment. For all doses of radiation, we would predict a latent period before any decrease in the number of cells in this compartment is

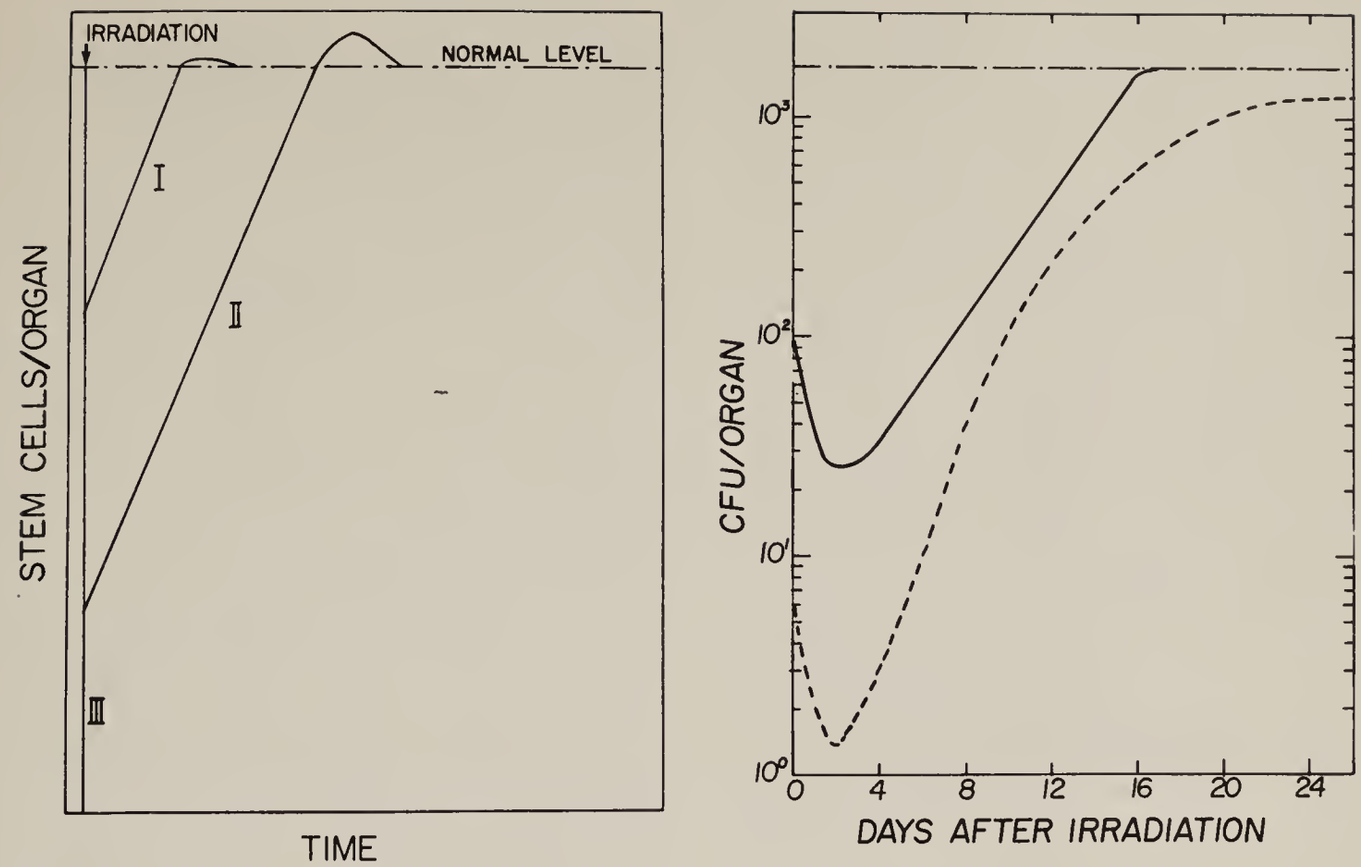

Fig. 3—The effect of various doses of ionizing radiation on the number of marrow stem cells as a function of time after irradiation. 3A) Theoretical prediction with I, II and III indicating the effects of low, moderate and high doses of radiation; 3B) Data from Valeriote *et al*[3] for 300 rads (solid) and 500 rads (dashed) of gamma radiation.

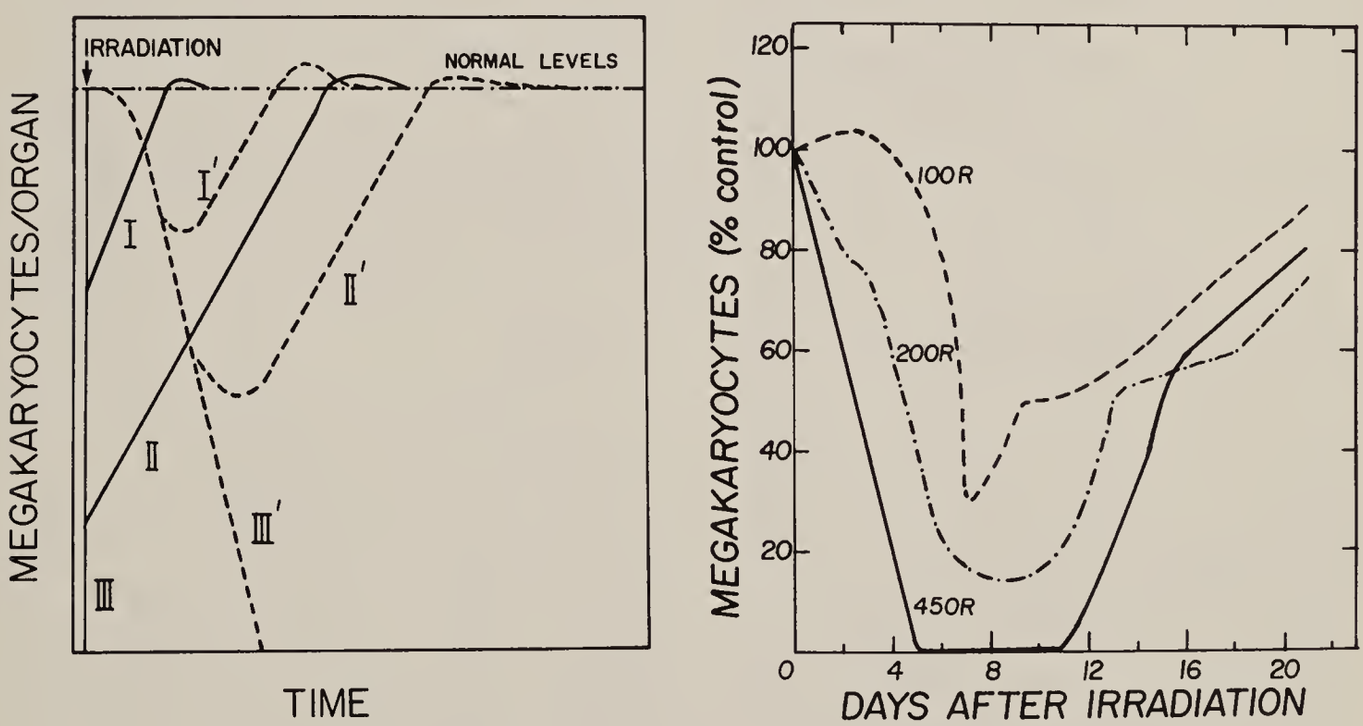

Fig. 4—The effect of various doses of ionizing radiation on the number of marrow megakaryocytes in mice. A) Theoretical prediction with solid lines representing effects on marrow CFU-S (from Fig. 3A) and dashed lines the effects on megakaryocytes with I', II' and III' as in Fig. 3A; B) Data from Simpson[4] following 100 rads (dashed), 200 rads (dot-dash) and 450 rads (solid) of x-rays.

observed to occur. The length of this latent period (and in fact whether it exists or not) is dependent upon 1) the rate at which cells enter and leave the differentiating compartment, that is, their cellular turnover time; and 2) the size of the precursor pool. If cells turn over very rapidly then one also would expect to deplete this compartment quite rapidly since there would be a severely decreased cellular input from the irradiated stem cell compartment. However, if the turnover time is relatively long, then a sizable latent period would be expected. If the turnover time were very long in comparison to the recovery time of the stem cells then one might not even observe a decrease in the number of differentiated cells in the time interval between the depletion and recovery of the stem cell compartment. In Fig. 4A we have allowed an initial latent period in cases I′ and II′ following which there is a decrease in the number of differentiated cells with subsequent recovery in this compartment as a consequence of the recovery of the stem cell compartment. The stem cell recovery results in the number of differentiated cells reaching the previous steady-state level. In the case of the complete destruction of the stem cell compartment (III′), the differentiating compartment would decrease at a rate approximating the rate of cell exit and would, of course, never recover.

One compartment which we have not discussed and which will affect the kinetics of both decline and recovery of the differentiated compartment, is the post-stem-cell amplification compartment lying between the stem and differentiated compartments. Although Jackson[2] may have developed a specific cytochemical test for cells in this compartment, there are no reported data on the effects of irradiation on these precursors which have been obtained directly. Simpson,[4] however, indirectly estimated a D_0 for this compartment of approximately 170 rads with little or no shoulder by plotting a dose survival curve for the number of megakaryocytes present seven days after a whole-body radiation dose as a function of the dose. This value is interesting when compared to a D_0 of approximately 100 rads that has been reported for CFU-S.[5] Since it is known that the least mature megakaryocytes are replicating their DNA, it is reasonable to assume that the preceeding unidentified precursors are also mostly in DNA replication and thus relatively sensitive to radiation. The larger D_0, however, may indicate that the process of nuclear endoreduplication (or endomitosis) which is unique to megakaryocytes may also be less susceptible to a radiation-induced inhibition of DNA synthesis leading to cell reproductive death. Alternatively, this compartment may be composed of diploid cells that are mostly in a noncycling, or G_0, state which respond to a normal demand for megakaryocytes solely by differentiation and to an accelerated demand by both proliferation and differentiation. In these cases, the precursor compartment would be relatively radioresistant and thus continue to provide recognizable megakaryocytes for some period of time even after low doses of radiation. After larger doses of radiation, many of these precursors would be forced into cell cycle and thus be susceptible to reproductive death. Precise knowledge concerning the number of cells in this precursor compartment and the proportion in cell cycle under steady-state conditions and those following irradiation, is necessary before we can predict with any certainty the recovery of the more differentiated megakaryocyte compartments.

As shown in Fig. 4B, the number of megakaryocytes in the recognizable cell compartment does not decrease for the first few days after exposure to low doses of radiation (100 rads); in fact, it may even rise above normal. The higher the dose of radiation, however, the sooner the megakaryocyte count is observed to decline so that after higher radiation exposures (450 rads), bone marrow megakaryocytes are undetectable by about five days after irradiation. As to whether the decrease in the number observed previously was due to mature or immature cells, it can be seen from Fig. 5 that following

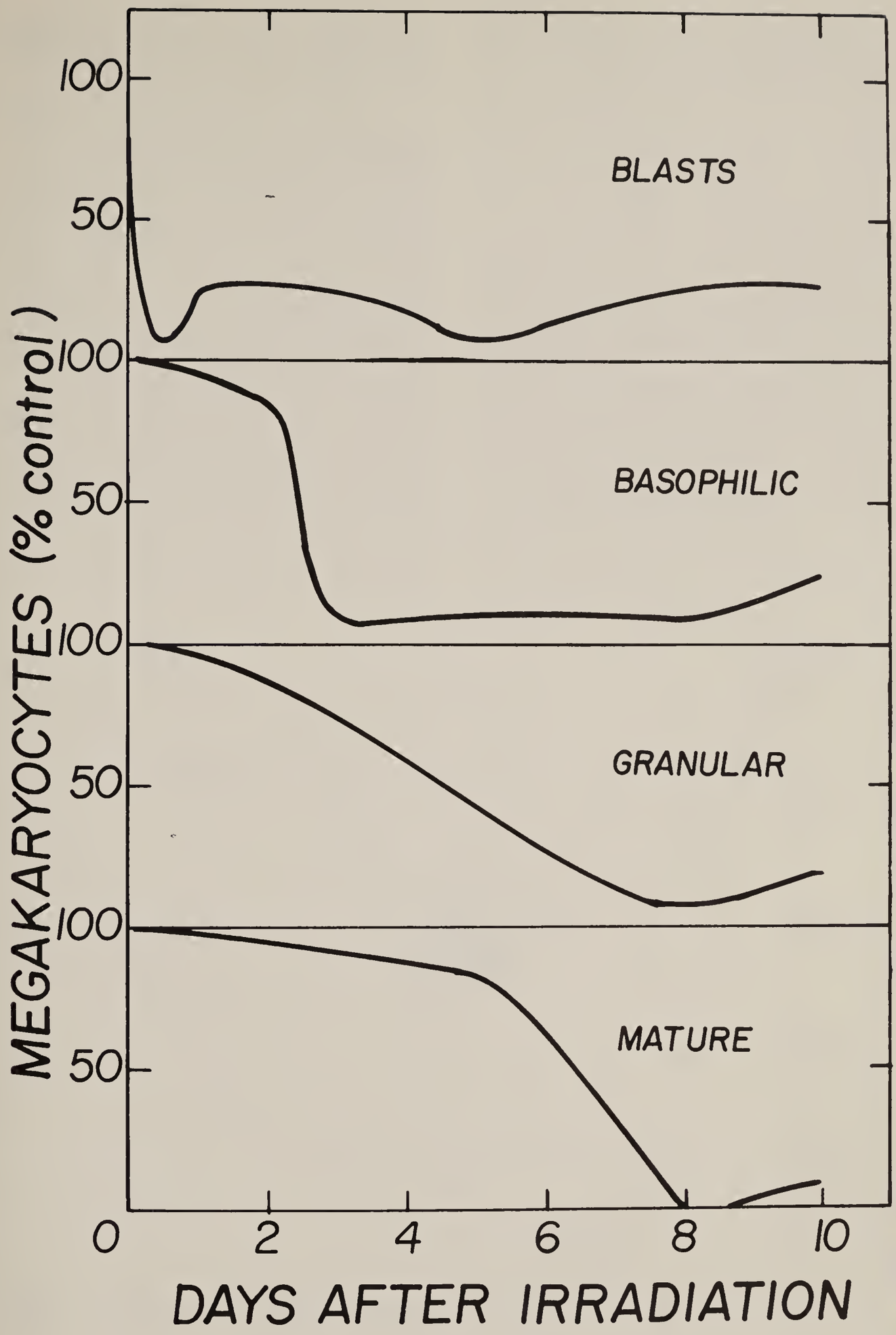

Fig. 5—Change in the number of megakaryocytes of various maturation stages in rat marrow as a function of time after 200 rads of x-rays. Data from Simpson.[4]

an exposure of 200 rads, a rapid decline in the number of megakaryoblasts, the youngest recognizable megakaryocytes, is observed which reaches minimal values within six hours. At later periods after irradiation, numbers of the more mature megakaryocytes begin to disappear with the mature reaching undetectable levels on the eighth day.

Changes in the platelet counts can be predicted from the fact that platelets, being fully differentiated and incapable of proliferation, are relatively radioresistant. As shown in Fig. 6, changes in the number of platelets in the peripheral blood circulation are similar to those in megakaryocytes in the marrow (i.e. the higher the dose of radiation, the sooner the platelet number begins to decline) except that their decline lags 24 to 48 hours behind that of the precursor megakaryocytes.

The foregoing results are adequately explained by assuming that mature megakaryocytes are relatively insensitive to radiation and continue to differentiate and produce platelets after irradiation. Thus, platelet production by the more mature megakaryocytes continues for some interval of time approximating the megakaryocytes' transit time. During this period, the megakaryocyte population itself declines both from the lack of entry of new cells and the loss of mature megakaryocytes through platelet production until finally no new platelets are produced. Maturing megakaryocytes would be less susceptible

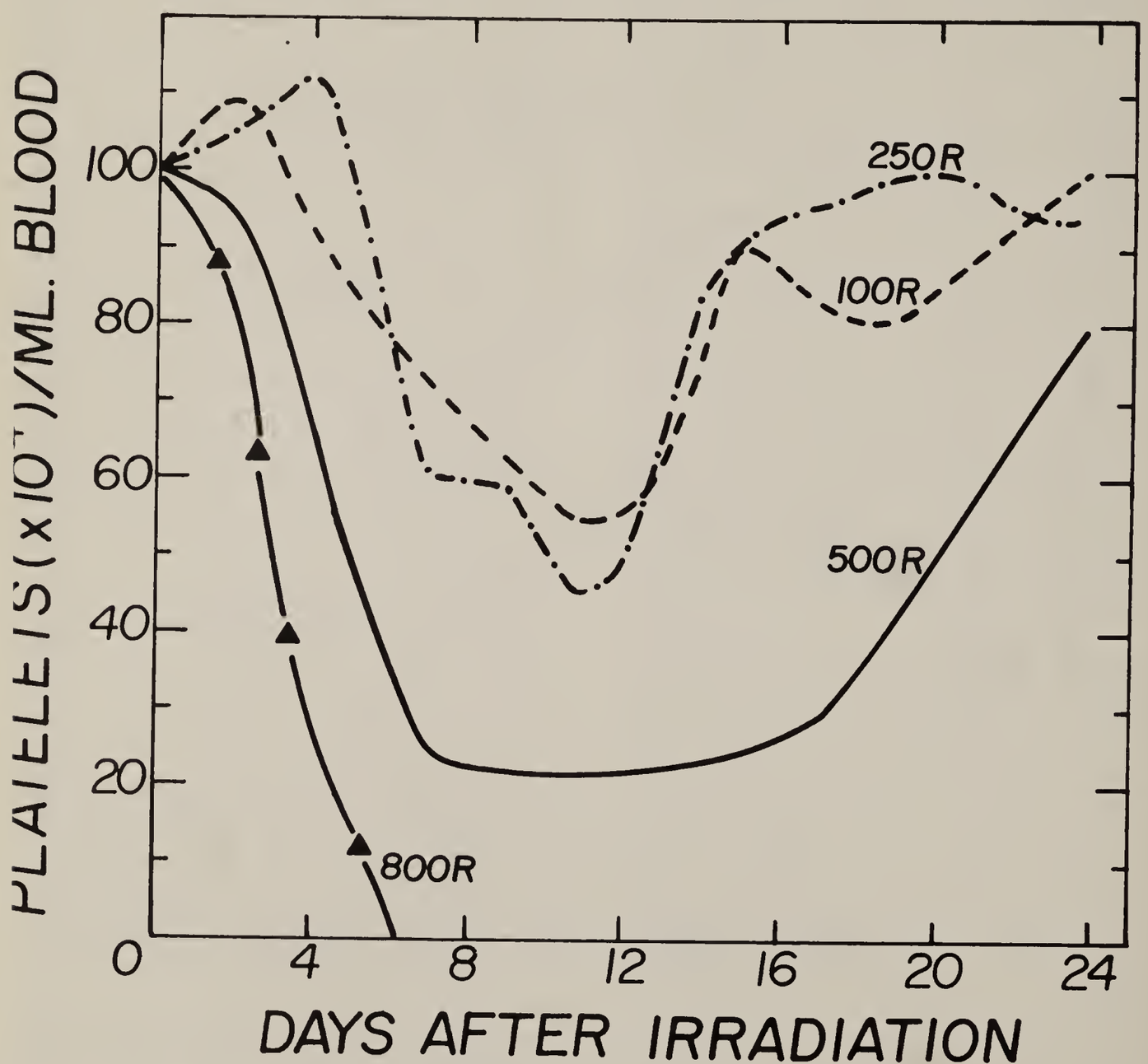

Fig. 6—Change in the number of peripheral blood platelets in mice exposed to various doses of onizing radiation. Data from Ref. 6.

to radiation damage and thus megakaryocytes in later stages of differentiation presumably would be able to continue their maturation unhindered.

In conclusion, it is clear that the model of the stem cell-megakaryocyte-platelet system is important and useful since it can predict with some accuracy the sequence of cellular changes which occurs following irradiation. It is reasonable to believe that this model would also be predictive of the effects following the administration of various chemotherapeutic agents. We are presently testing several drugs for their effects on precursor cells, both pluripotential and those committed to erythropoiesis and granulopoiesis as well as megakaryocytopoiesis. The building of biology models is most important to the clinician if the information derived can be applied in a constructive fashion. Hopefully knowledge obtained with this system will permit its manipulation in such a manner that more effective anticancer therapy can be carried out.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Anesthesiology

Sadove MS, Thomason RD, Jobgen E: *Capillary versus arterial blood gases. Anesth Analg (Cleve) 52:724, 1973*

Evaluation of a patient's blood gas status cannot be made by just looking at the patient. Oftentimes due to the critical condition of the patient and the rapid changes which occur with therapy and/or progression of the diseased state, multiple blood samples must be obtained. The complications resulting from arterial puncture, although rare, are nevertheless significant, and in infants the volume of blood necessary for study becomes a critical factor in multiple determinations.

Micro-sample determinations of blood gas parameters are available from most equipment manufacturers; therefore, the sampling itself is the only hurdle which needs to be overcome. In this article it is shown that micro-sampling from an earlobe puncture is a simple, safe, and readily accessible method of obtaining accurate blood gas parameters. The earlobe must first be prepared by warming, flicking of the earlobe to obtain flushing and then wiping with an antiseptic swab. A deep puncture wound with a 20-gauge hypodermic needle is then made to obtain free flow of blood from the lateral dependent margin of the lobe. The lobe is then wiped dry with a cotton swab to permit drop formation and a 100-ml heparinized capillary tube inserted to the center of the drop and filled with blood flowing from the puncture side, avoiding air bubbles. The capillary tube is then transferred to the microanalysis equipment and values obtained.

Results compared with arterial punctures done at the same time gave the following: mean difference – pH values of 0.00634 with 95 percent confidence limits of 0.066 and 0.078, PO_2 0.19 mm Hg with 95 percent confidence limits of 1.304 and 1.692 mm Hg and for PCO_2 1.436 mm Hg with 95 percent confidence limits of 2.46 and 0.411 mm Hg. These differences are not clinically significant and would indicate that this is a technique which should be utilized to a much greater degree.

Biochemistry

Booyse FM, Guiliani D, Marr JJ, Rafelson, ME Jr: *Cyclic adenosine 3', 5'-monophosphate dependent protein kinase of human platelets: Membrane phosphorylation and regulation of platelet function. Ser Haemat 6:351, 1973*

Protein kinase-catalyzed phosphorylation reactions are involved in contractile protein function as well as membrane permeability control and ion flux. cAMP dependent protein kinases exist as nonactive holoenzyme complexes (CR) and can be dissociated by cAMP, into a cAMP-binding (cAMP•R) and cAMP catalytic subunit (C).

The major cAMP dependent protein kinase of human platelets has been purified from platelet membranes by DEAE-cellulose and BioGel chromatography. The apparent molecular weights of the CR, C, and cAMP•R units are 140,000, 85,000 and 30,000 daltons, respectively. Treatment of the cAMP•R subunit with cAMP results in further dissociation into two 14,000 dalton and finally, four 7,500 dalton units. The purified kinase (C) will phosphorylate an exogenous protein receptor such as histone as well as a natural platelet membrane associated endogenous protein receptor. This natural platelet membrane receptor has been purified and has a molecular weight of about 84,000 daltons, consisting of two 44,000 dalton subunits. Phosphate is incorporated into this protein in the form of phosphoserine and phosphothreonine. This incorporation is inhibited by ADP

and thrombin, but not affected by PGE_1 and epineprine. Platelet membranes (receptor protein), labeled with γ-^{32}P-ATP, rapidly transfers the labeled phosphate to added ADP. Thrombin causes the rapid release of labeled phosphopeptides. High levels of membrane (surface?) phosphorylation appears to maintain the platelets in a non-aggregating state, and we propose that the rapid dephosphorylation of the platelet surface is the common reaction that leads to membrane changes (*cis*- and *trans*-membrane effects), cytogel extrusion and subsequent platelet aggregation.

Hofer C, Bezkorovainy A, Saba TM: *A model for R.E.S. blood clearance involving Michaelis-Menten kinetics. Physiol Chem Physics 5:515, 1973*

The clearance of foreign material from blood circulation by the reticuloendothelial system (R.E.S.) is generally represented by a simple exponential function which, however, is unable to account for many experimental observations. In order to provide a more useful model for the representation of clearances of foreign material from blood, clearance was considered to be a function of two consecutive processes and was thus amenable to a treatment by the Michaelis-Menten procedure that is generally used in enzyme kinetics studies. The differential form of the Michaelis-Menten equation furnishes the explanation for the dose dependence, which is a saturation phenomenon. The integrated form of the equation is

$$C(t) = C(O)e^{-kt}\, e^{b}\, [C(O) - C(t)],$$

where

$$k = \frac{k_2 E_T}{km} \text{ and } b = \frac{1}{km}$$

and where $C(O)$ is the initial colloid concentration, $C(t)$ is the colloid concentration at time t,k_2 is rate constant characterizing phagocytosis, E_T is the total opsonin concentration, and km is the Michaelis-Menten constant for this system. It may be seen that the classical equation is merely the approximate solution of this equation. The empirical constant of the classical equation could now be expressed in either measurable quantities or in quantities of the R.E.S. components and could thus, in theory, be computed. Data from dogs injected with colloid were successfully applied to the proposed model.

McDonald RI, Shepro D, Rosenthal M, Booyse FM: *Properties of cultured endothelial cells. Ser Haemat 4:31, 1973*

Endothelial cells were obtained by several procedures from human, bovine and dog aortae and were successfully cultured *in vitro*. Cultures, established by 'thrombinizing' the vessel intima, were subcultured for 18 passages and were found to maintain their structural phenotype. The cells contained numerous granules, microfilaments, golgi complex, extensive rough and smooth endoplasmic reticulum, pinocytotic vesicles, and intercellular modifications such as tight junctions. Furthermore, these cells undergo rapid shape change after treatment with thrombin and less extensive morphological changes following treatment with epinephrine, ADP and endotoxin. Of particular significance is that the cultured endothelial cells have fibrinolytic activity and contractile protein immunologically indistinguishable from platelet thrombosthenin.

Nichols JH, Bezkorovainy A: *Isolation and characterization of a glycoprotein from human colostrum. Biochem J 135:875, 1973*

A glycoprotein was isolated from the M-1 acid glycoprotein fraction of human colostrum. It had a molecular weight of 31200 and contained 27 percent galactose, 21.7 percent hexosamine, 8.0 percent fucose and 10.8 percent sialic acid by weight. The glycoprotein had no absorption maxina in the 240 to 300 nm region, and was virtually free of ABH(O) and M and N blood-group activity. Alkaline borohydride cleavage of the glycoprotein resulted predominantly in the destruction of threonine and galactosamine

Rafelson ME Jr, Hoveke TP, Booyse FM: *The molecular biology of platelet-platelet and platelet-endothelial interactions. Ser Haemat 6:367, 1973*

With the technique of shadow-casting and scanning electron microscopy of whole platelets and cultured endothelial cells, it has been possible to observe both the very early events produced by thrombin action on these cells and also what appears to be the entire process of *in vitro* platelet-endothelial interaction. Treatment of both platelets and endothelial cells with thrombin for 1 to 12 seconds results in a very rapid and extensive extrusion of the cytogels of these cells with a concomitant change in both platelet and endothelial cell size and shape. The data presented here show that platelet and endothelial cell membranes do not directly participate in the early events preceding and leading to platelet-endothelial cell interactions. It is the extruded platelet and endothelial cell cytogels that appear to interact to form intercellular attachment. Subsequent cellular membrane interactions and dissolution appear to follow the contraction of the interacting cytogels which brings the platelets and endothelial cells into close contact. A new relaxation-contraction model is proposed to accommodate the early sequence of events preceding and leading to platelet-endothelial cell interactions.

Springer GF, Adye JC, Bezkorovainy A, Murthy JR: *Functional aspects and nature of the lipopolysaccharide-receptor of human erythrocytes. J Infect Dis 128:5202, 1973*

We have isolated for the first time from human erythrocytes a physicochemically homogeneous lipo-glycoprotein that is rich in neuraminic acid, has a molecular weight of 228,000 and prevents attachment to erythrocytes of unheated and heated, smooth and rough endotoxin of all gram-negative bacteria tested. It did not interact with other bacterial antigens and, therefore, is named "lopopolysaccharide-receptor." The receptor activity is destroyed by proteases; lipid and neuraminic acid are not involved in the activity. We have established quantitatively with radioactive tracers that the receptor interacts with lipopolysaccharides and not with receptors on erythrocytes. The receptor blocks those lipopolysaccharide groupings that attach to erythrocytes. The action of the receptor is physical and reversible; it removes lipopolysaccharides fixed to red cells. While other compounds (namely, glycolipids, lipoproteins, and basic proteins) also inhibit attachment of lipopolysaccharide to cells, they are much less active, and those tested are unspecific.

Wong KC, Kornel L, Bezkorovainy A, Murphy BEP: *Isolation of cytoplasmic glucocorticoid-binding protein(s) from rat liver by means of affinity chromatography, and its partial characterization. Biochim Biophys Acta 328:133, 1973*

Intracellular corticosteroid-binding protein(s) was isolated from rat liver cytosol by means of affinity chromatography, using aminosepharose coupled to cortisol hemisuccinate. This protein material displayed apparent homogeneity on Sephadex G-100 and G-200 gel filtrations. Its molecular weight is 93 000 (average of two estimations), as calculated from sedimentation and diffusion constants. The amino acid composition of this protein closely resembles that of transcortin, although some quantitative differences between the two exist. The carbohydrate content of this protein was found to be appreciably smaller than that of transcortin. Calculation of the amount of possible contamination of the isolated protein(s) with residual blood present within the vascular bed of the liver tissue prior to homogenization indicates that, at most, one-fourth of the cytoplasmic corticosterone-binding protein(s) could be due to contamination with transcortin from plasma. On starch gel and polyacrylamide gel electrophoresis, the isolated protein material resolved into two major and one minor components, migrating in the α_1- β_2- globulin region. Competitive binding studies with different steroids revealed that the isolated protein(s) has high affinity for progesterone, corticosterone, and cortisol. For all the three steroids, at least two binding components were present on the

Scatchard plot: one possessing high affinity but low capacity ($K_A = 10^{-8}$ M, $n = 15 \cdot 10^{-9}$ M), the other, lower affinity but higher capacity ($K_A = 10^{-6}$ M, $n = 160 \cdot 10^{-9}$ M).

Wong KC, Kornel L, Bezkorovainy A, Murphy BEP: *Isolation of cytoplasmic glucocorticoid-binding protein(s) from rat liver by means of affinity chromatography, and its partial characterization. Biochim Biophys Acta 328:133, 1973*

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Cardiology

Barresi V, Susmano A, Colandrea MA, Bogdonoff ML, Muenster JJ: *Congenital absence of the circumflex coronary artery. Am Heart J 86:811, 1973*

Two patients found to have congenital absence of the circumflex coronary artery are reported. The clinical, electrocardiographic, vectorcardiographic, and cineangiographic findings are presented. No distinctive clinical or laboratory abnormalities were found except for the unusual anatomical posterior origin of the ostium of the main left coronary artery.

Cardiovascular Thoracic Surgery

Faber LP, Monson DO, Amato JJ, Jensik RJ: *Flexible fiberoptic bronchoscopy. Ann Thorac Surg 16:163, 1973*

The flexible fiberoptic bronchoscope has become an invaluable diagnostic and therapeutic instrument in the management of pulmonary disease. Advantages over the conventional rigid bronchoscope include airway examination to the subsegmental level, increased accuracy of diagnosis in pulmonary malignancy, patient comfort, ease of bedside examination, and atraumatic aspiration of postoperative secretions. Disadvantages include cost, inability to remove foreign bodies, and lack of a satisfactory technique for infant endoscopy. The extended range of diagnostic and therapeutic capabilities of the flexible bronchoscope makes it an important instrument for the thoracic surgeon.

Najafi H: *Aneurysm of cystic medionecrotic aortic root. J Thorac Cardiovas Surg 66:71, 1973*

This report concerns two patients with aortic root aneurysm in whom the right coronary orifice was significantly displaced superiorly due to aneurysmal dilatation of the right coronary sinus of Valsalva. The left coronary orifice was in near normal proximity to the valve ring. Surgical treatment consisted of resecting the aneurysm and leaving only a 1 cm aortic cuff. This was not done in the region of the left coronary orifice, for the transection line was distal to this orifice. Therefore, the right coronary artery was transplanted to the ascending aortic graft with the use of a short segment of autogenous saphenous vein. The aortic valve was replaced with a Björk-Shiley prosthesis.

Genetics and Human Devolpment

Frischer H, Nelson R, Noyes C, Carson PE, Bowman JE, Rieckmann KH, Ajmar F: *NAD(P) Glycohydrolase deficiency in human erythrocytes and alteration of cytosol NADH-methemoglobin diaphorase by membrane NAD-gycohydrolase activity. Proc Nat Acad Sci USA 70:2406, 1973*

Erythrocytic NADH methemoglobin diaphorase acquires NADH-dichlorophenolindophenol diaphorase activity when enzyme-associated NAD is removed. This transformation is reversible and can be mediated by membrane NAD glycohydrolase (EC 3.2.2.5) in hemolysates as well as in intact cells exposed to hydrogen peroxide. It is abolished either in NADH methemoglobin diaphorase deficiency or in NAD(P) glycohydrolase (EC 3.2.2.6) deficiency which is common in Afro-American but not in European-American adults. Activities of erythrocytic NADP glycohydrolase and NAD glycohydrolase appear to depend on a single membrane enzyme.

Hartz J, El Maghrabi R, Namen A, Gabr M, Bowman J, Carson P, Ajmar F, Kamel K: *Enzyme studies in glucose-6-phosphate dehydrogenase deficient erythrocytes from Egyptians, Italians, and American Negroes (pyrophosphatase, 6-phosphogluconate dehydrogenase, glutamic-oxalacetic transaminase, acid phosphatase, catalase and superoxide dismutase assays). Clin Chim Acta 48:117, 1973*

American Negro adults, Italian adults, and Egyptian children all with hemizygous glucose-6-phosphate dehydrogenase (G6PD) deficiency but without recent oxidant challenge, exhibited normal erythrocyte catalase and acid phosphatase phenotypic activities, normal immunochemically determined levels of erythrocyte catalase and superoxide dismutase, and normal or slightly increased erythrocyte glutamicoxalacetic transaminase and 6-phosphogluconate dehydrogenase activities. Similar erythrocyte pyrophosphatase activities were found in hemizygous and normal adult Negroes and Italians and in hemizygous Egyptian children, but lower activities were found in normal Egyptian male children. Egyptian heterozygotes for G6PD deficiency generally exhibited normal values in the above assays. Erythrocyte aicd phosphatase phenotypes were determined in 73 Egyptians yielding the following gene frequencies: $P^a = 0.24$, $P^b = 0.73$, and $P^c = 0.03$. Similar statistically indistinguishable gene frequencies were found in normal and in favitic Egyptian male children.

Smith GF, Sachdeva S, Justice P: *A chromosomal break and partial delection of a number 9 chromosome. Hum Hered 23:561, 1973*

A male infant was observed with a complex of unusual clinical abnormalities. Chromosomal studies revealed that the child was mosaic for a chromosomal fragment from the long arms of a number 9 chromosome. The majority of cells contained 46 chromosomes with a partially deleted number 9 chromosome and chromosomal fragment. From these

data and others reported, it would appear that there is a susceptibility for breakage of the long arms of the number 9 chromosome at the junction of the heterochromatin and euchromatin area closest to the centromere. The lymphocytes from this child are capable of transformation into long-term lymphocyte cultures, and after many months in culture the chromosomal fragment has replicated in the cultured cells even though it contained no detectable centromere.

Gynecologic Oncology

Piel IJ, Slayton RE, Perlia CP, Wilbanks GD: *Combination chemotherapy with bleomycin and methotrexate in recurrent and disseminated cervical carcinoma: a preliminary study. Gynecol Oncol 1:184, 1973*

The toxicity and effectiveness of a combination of bleomycin and methotrexate was studied in eight patients with metastatic or recurrent squamous cell carcinoma of the cervix. Three patients had disappearance of measurable disease, two had measurable decrease in volume of tumor, and one had symptomatic improvement without measurable change in lesions. Major toxicity included stomatitis, diarrhea, and hyperpigmentation. Case reports of complete responders are presented.

Hematology

Bacus JW: *The observer error in peripheral blood cell classification. Am J Clin Pathol 59:223, 1973*

An estimate of the observer classification error was obtained for six classes of peripheral blood leukocytes: lymphocytes, segmented and band neutrophils, eosinophils, basophils, and monocytes. The images, in the form of colored photomicrograph transparencies, were classified independently by 11 senior hematology technicians. The consensus was used to obtain a classification "truth" for each image, and each classification result was then compared with this "true" classification to obtain error rates. When the segmented and band neutrophils were lumped together as one class, the resulting average observer error per class for the consolidated five classes was approximately one percent. The error in classifying segmented *versus* band neutrophils was estimated at about seven percent per class for those observers with the least systematic bias toward naming one of these cell types preferentially.

Infectious Diseases

Edwards LD, Levin S, Balagtas R, Lowe P, Landau W, Lepper MH: *Ordering patterns and utilization of bacteriologic culture reports. Arch Intern Med 132:678, 1973*

During a two-week period, all inpatient bacteriologic culture reports (1,381) were monitored, and ongoing chart review was conducted for all newly admitted patients (436) who had cultures taken; 17 percent of the infections had no cultures taken when indicated. The average bacteriology laboratory cost to each of these 436 patients was $37.16. Total antimicrobial drug costs were estimated to be $41,700.

Of cultures ordered for suspected infections in the medical and surgical services, 24.5 percent yielded positive results. Patients were already taking antimicrobial drugs when one-third of the cultures were obtained. Immediate Gram stains were done 3.5 percent of the time. In only 20.9 percent of positive cultures with one or more isolates, 1.4 percent of negative cultures, or 7.0 percent of all cultures was a change made in therapy. There was no consistent logical approach to the use of bacteriological culture results.

Deinhardt F, Wolfe L, Massey R, Hoekstra J McDonald R: *Simian sarcoma virus: oncogenicity, focus assay, presence of associated virus, and comparison with avian and feline sarcoma virus-induced neoplasia in marmoset monkeys. Bibl Haemat 39:258, 1973*

Simian sarcoma virus, type I *(Lagothrix)* (SSV-I) was grown and quantitated in cell cultures and a nontransforming associated virus (SSAV-I) was identified. The transforming virus induced well differentiated fibrosarcomas in marmoset monkeys and the tumor cells contained group specific antigen and produced both SSV-I and SSAV-I. The degree of virus genome expression in SSV-I induced marmoset tumors was compared to virus expression in sarcomas induced in marmosets by avian and feline sarcoma viruses.

Goodman NC, Ruprecht RM, Sweet RW, Massey R, Deinhardt F, Spiegelman S: *Viral-related DNA sequences before and after transformation by RNA tumor viruses. Int J Cancer 12:752, 1973*

Marmoset monkey fibroblasts transformed by non-indigenous RNA tumor viruses (RSV or FeSV) acquire viral DNA sequences not present in normal cells. The newly gained sequences are always related to those of the transforming virus, a result in agreement with the proviral hypothesis. In contrast, the nucleic acid of the indigenous simian RNA tumor virus, SSV-1, exhibits partial homology with the DNA of normal marmoset fibroblasts as well as with SSV-1 transformed cells. Since a similar situation has been observed with avian and lower mammalian systems, it would appear that homology with normal cellular DNA can be used to provide a tool for determining the species of origin of newly isolated RNA tumor viruses.

Hull RN, Dwyer AC, Holmes AW, Nowakowski E, Deinhardt F, Lennette EH, Emmons RW: *Recovery and characterization of a new simian herpesvirus from a fatally infected spider monkey. J Natl Cancer Inst 49:225, 1972*

A 5½-month-old, zoo-born and reared spider monkey became ill and died. Examination of the dead animal disclosed numerous crusty brownish lesions on the lips and nose and large, deeply ulcerated areas on the tongue, palate, and gums. Necropsy also showed pneumonitis, congestion of the meninges, and skin ulcerations in the axillae and on the back. Brain tissue was inoculated into cell cultures, and a cytopathic agent was recovered. This agent has the physico-chemical properties of a herpesvirus and also the appearance of a herpesvirus when studied by electron microscopy. Extensive serological study shows that it has a relationship to marmoset herpesvirus, though it is not antigenically identical to it. Study of antibody patterns in New World monkeys shows that the spider monkey agent and the marmoset agent have different host distributions in nature, with the squirrel monkey serving as the primary reservoir for the marmoset agent, and the spider monkey for the spider monkey agent. There is as yet no knowledge of the pathogenesis of infection with the spider monkey agent in man. It appears clearly to be a new member of the herpesvirus family.

Marczynska B, Shramek G, Wolfe L: *Herpesvirus saimiri: a simian counterpart of Epstein-Barr virus of man? Bibl Haematol 39:417, 1973*

Herpesvirus saimiri (HVS), an indigenous virus of squirrel monkeys, was described first by Melendez *et al.* in 1968. In the early studies no overt clinical disease was observed in squirrel monkeys inoculated with HVS (Melendez *et al.*, 1969B) but it is unclear whether the animals used for these studies had HVS antibodies at the time of inoculation. In contrast, inoculation of HVS caused lymphomas of reticulum cell type in cottontopped

marmosets (CT) *(Saguinus [Oedipomidas] oedipus)*, white-lipped marmosets (WL) *(S. nigricollis* and *S. fuscicollis)* (Falk *et al.*, 1970, 1971; Wolfe *et al.*, 1971), owl monkeys *(Aotus sp.)* (Melendez *et al.*, 1969a), cinnamon ringtail monkeys *(Cebus albifrons)* (Melendez *et al.*, 1970) and possibly also in rabbits (Daniel *et al.*, 1970). The development of a more leukemia-like disease after inoculation of HVS into owl monkeys (Melendez *et al.*, 1971; Ablashi *et al.*, 1971) and WL marmosets (Wolfe *et al.*, 1971) was also described. The morphology, and physical and chemical characteristics identified HVS as a typical herpesvirus (Melendez *et al.*, 1968, 1969; Goodheart, 1970; Morgan *et al.*, 1970). Growth characteristics of HVS in cell cultures were studied by observation of cytopathic effects, development of typical large and small plaques, development of viral particles by electron microscopy (EM), and development of viral antigens by fluorescent antibody (FA) staining (Falk *et al.*, 1970, 1971). These, and associated studies, are reported and discussed in this presentation.

Theilen GH, Wolfe LG, Rabin H, Deinhardt F, Dungworth DL, Fowler ME, Gould D, Cooper R: *Biological sudies in four species of nonhuman primates with simian sarcoma virus* (Lagothrix) *Bibl haemat 39:251, 1973*

C-type virus was demonstrated in the tissues of a three-year-old woolly monkey *(Lagothrix)* with multiple fibrosarcomas. Eleven newborn and two fetal monkeys of four different species were inoculated with low speed centrifugation cell extracts. Of this group, a white-moustached marmoset developed a fibromatous lesion, but C-type virus was not demonstrated by electron microscopy in this tissue. Four newborn monkeys of two different species were inoculated with differential centrifugation cell extracts. Of this group, a white-lipped marmoset developed a well differentiated fibrosarcoma 30 days after inoculation. C-type virus was found in this tumor which was similar to that found in the original woolly monkey tumor.

Orthopedic Surgery

Belytschko TB, Andriacchi TP, Schultz AB, Galante JO: *Analog studies of forces in the human spine: computational techniques. J Biomech 6:361, 1973*

A mathematical model is developed for three-dimensional force analysis of the human vertebral column. The vertebrae are idealized as rigid bodies, while the discs, ligaments, and connective tissues are represented by deformable elements. An incremental stiffness method which accounts for nonlinearities due to large displacements is used. Preliminary results are presented for the behavior of an isolated, ligamentous column under traction, lateral loads, and compressive loads which result in buckling.

Galante J: *Total hip replacement. Orthop Clin North Am 2:139, 1971*

Total joint replacement is a valuable new procedure in orthopedic surgery. The low friction arthroplasty of Charnley and the Charnley-Müller prosthesis are discussed. Sixty-six operations performed at the University of Illinois Hospital between June 1968 and January 1970 are evaluated. Satisfactory results in relief of pain and ability to walk were obtained in over 90 percent of the patients.

Wound infection was a major disaster, an incidence of 6.6 percent. Ten patients required reoperations, three for replacement of a loose prosthesis, two for rewiring of the trochanter, three for removal of trochanteric wires, and two for removal of the prostheses after wound infection.

The indications and contraindications are discussed as well as the relative merits of both techniques.

Proper attention to the indication guidelines and to technical details are essential to insure good results.

Pathology

Eisenstein R, Larsson SE, Sorgente N, Kuettner KE: *Collagen-proteoglycan relationships in epiphyseal cartilage. Am J Pathol 73:443, 1973*

Columnar and hypertrophic zones of calf scapular cartilage were studied before and after extraction with 3 M guanidinium chloride (GuCl) and digestion with enzymes which degrade various components of the extracellular matrix. Morphologic and chemical analysis suggests that there are at least two anatomic pools of proteoglycan in this tissue. One, which resides between collagen fibrils, is extractable with GuCl. Another appears attached to collagen by strong bonds and is apparently not extractable with GuCl. This type of collagen-proteoglycan relationship is possibly restricted to epiphyseal cartilage. The morphology of the lacuna is different in the columnar and hypertrophic zones. Proteoglycans in the distal hypertrophic zone are less resistant to GuCl extraction.

Pharmacology

McCloy RB, Prancan AV, Nakano J: *Circulatory and respiratory effects of different mixtures of prostaglandins E_2 and $F_2\alpha$. Clin Res 21:437, 1973*

It was postulated that either prostaglandin E_2 (PGE_2) or $F_2\alpha$ is formed preferentially from the common precursor, arachidonic acid, in inflammation and bronchial asthma. This study was made to compare the circulatory and respiratory responses to different mixtures of PGE_2-$PGF_2\alpha$ (10:1, 1:1, 1:5) in dogs anesthetized with pentobarbital. As shown previously, PGE_2 (0.25-4 μg/kg) *per se* caused marked dose-related decreases in systemic arterial pressure (SAP) and slightly decreased both pulmonary arterial pressure (PAP) and pulmonary airway pressure (PAWP). On the other hand, $PGF_2\alpha$ (0.5-8 μg/kg) caused dose-related increases in SAP, PAP and PAWP. When geometrically increasing doses of the three mixtures of PGE_2 (0.25-4 μg/kg)-$PGF_2\alpha$ (0.025-8 μg/kg) were given, SAP always decreased essentially in proportion to the dose of PGE_2. In contrast, both PAP and PAWP increased essentially in proportion to the dose of $PGF_2\alpha$. This study indicates that, with wide ranges of different mixtures of PGE_2-$PGF_2\alpha$, the systemic peripheral vascular bed was considerably more sensitive to PGE_2 than $PGF_2\alpha$, while both the pulmonary vascular bed and the bronchial tree were more sensitive to $PGF_2\alpha$ than PGE_2. Hence, the prostaglandins have unique tissue specificity even if equimolar amounts of PGE_2 and $PGF_2\alpha$ are formed in the pathological disorders. This suggests that the alleged preferential biosynthesis of PGE_2 or $PGF_2\alpha$ is not *sine qua non* for the pathological manifestations of inflammation or bronchial asthma.

McCloy RB, Prancan AV, Nakano J: *Direct effects of ethanol and acetaldehyde on the coronary circulation and myocardial contractile force in dogs. Clin Res 21:437, 1973*

It has been well established that the circulatory effects in acute ethanol (EtOH) intoxication are caused by EtOH *per se* and its metabolite, acetaldehyde (ALD). The present study was undertaken to investigate the direct effects of EtOH and ALD on the coronary blood flow (CBF) and myocardial contractile force (MCF) in dogs anesthetized with pentobarbital. The blood flow of the anterior descending branch (ADB) of the left coronary artery was cannulated and perfused at a constant rate with aterial blood by means of Sigmamotor pump. MCF in the area perfused by the ADB was measured by a Walton-Brodie strain gauge arch. The injection of EtOH (0.25-2 mg/kg) into the ADB

caused a dose-related decrease in ADB perfusion pressure (ADBPP) and MCF without any significant change in systemic arterial pressure (SAP), left atrial pressure (LAP) and heart rate (HR). In contrast, the injection of ALD (0.25-2 mg/kg) into the ADB decreased ADBPP but caused a biphasic change in MCF, an initial rapid increase being followed by a decrease. The prior i.v. injection of propranolol (1 mg/kg) or reserpine (0.25 mg/kg for three days) abolished the positive inotropic action of ALD without any change in ADBPP. This study indicates that EtOH exerts a negative inotropic action and this decreases the coronary vascular resistance. In contrast, ALD increases MCF by releasing cardiac norepinephrine, and causes coronary arteriolar dilatation.

McCloy RB Jr, Prancan AV, Nakano J: *Cardiovascular actions of acetaldehyde in dogs. Clin Res 21:815, 1973*

It is well established that ethanol (EtOH) is metabolized to acetaldehyde (ALD) in the body. Since EtOH exerts a depressant effect on the isolated myocardium but increases heart rate (HR) and myocardial contractile force (MCF) in healthy humans or animals, it appears that the circulatory changes observed during EtOH intoxication may be due to both EtOH and ALD. The current study was undertaken to investigate the cardiovascular effects of ALD in anesthetized dogs. Systemic arterial pressure (SAP), pulmonary arterial pressure (PAP) and left atrial pressure (LAP) were measured with Statham pressure transducers. Cardiac output (CO), systemic venous return (SVR) and regional blood flow were measured with electromagnetic flow meters.

The i.v. injection of graded doses (2-16 mg/kg) of ALD caused dose-related increases in HR, SAP, PAP, CO SVR and MCF, while LAP decreased. The intraarterial injection of ALD constricted the peripheral vascular beds in the brachial, femoral, renal, carotid, and superior mesenteric arteries, and dilated those in the coronary and hepatic arteries. Phenoxybenzamine and propranolol not only blocked the cardiovascular effects of ALD but reversed its pressor effect. It is concluded that most of the hemodynamic effects of ALD resulted from the release of catecholamines from nerve endings and the adrenal medulla. Furthermore, this study suggests that the cardiovascular changes during early or moderate EtOH intoxication are mostly due to ALD.

Nakano J, Prancan AV: *Effect of prostaglandin E_1 and indomethacin on the survival of endotoxemic mice. Clin Res 21:815, 1973*

Prostaglandins (PGs) may act as the major chemical mediators for the pathogenesis and clinical manifestations of septic shock since plasma PG levels are elevated in this disorder. The present study was undertaken to examine whether the i.v. administration of prostaglandin E_1 (PGE_1) or indomethacin (IND), a potent PG synthesis inhibitor, would modify the survival rate of mice which received E. coli endotoxin (LD60). Adult mice were divided into three groups. To the first group (63 mice), the IND solvent alone was given intraperitoneally (i.p.); to the second group (25 mice), IND (1 mg/kg); and to the third group (24 mice), PGE_1 (100 μg/kg). All mice subsequently received endotoxin (10 mg/kg, i.p.) 30 min. after drug injection. In addition, the third group of mice received PGE_1 (50 μg/kg) shortly after the injection of endotoxin and then the same dose was repeated two hrs. later. The survival rate of mice was monitored every two hrs. for 48 hrs. It was found that 48 hrs. after endotoxin, 30.5 percent of controls and 39.5 percent of PGE_1-treated mice survived. In contrast, 82.5 percent of IND-treated mice survived. Thus, there was no significant difference in the survival rate between control mice and PGE_1-treated mice. On the other hand, a considerably larger number of IND-treated mice survived. This study suggests that the exogenous administration of PG does not significantly enhance the survival of endotoxemic mice. In contrast, the inhibition of PG synthesis by IND appears to be efficacious in this disorder.

Nakano J, Prancan AV: *Progstaglandin dehydrogenase activity in shock lungs and kidneys. Clin Res 21:887 1973*

Plasma prostaglandin (PG) levels were found to increase in septic shock. The present study was undertaken to examine the PG dehydrogenase (PGDH) activity in the lung and kidney of rats in endotoxin shock. Male Holtzman rats were treated with an intraperitoneal injection of saline (control) or of 10 mg/kg of E. coli endotoxin. Eight hours later systemic arterial pressure (SAP) was measured with a Statham pressure transducer. Thereafter, the rats were sacrificed and the lung and kidney removed. After differential centrifugation of the tissue homogenates, soluble fractions were harvested. PGDH activity was measured by the method described previously (Nakano *et al.* Biochem Pharmacol 20:2512, 1971).

It was found that eight hours after the injection of saline or endotoxin, SAP of control and endotoxemic rats were 121 $\pm$4 and 52 $\pm$6 mm Hg, respectively. The control lung and kidney homogenates metabolized approximately 90 and 75 percent of prostaglandin E_1 (PGE_1), respectively, within five minutes. In contrast, the shock lung and kidney homogenates inactive PGE_1 at markedly slower rates. Usually, the decreased PGDH activity was considerably greater in the lung than in the kidney. It is suggested that the increased PG levels found in animals with endotoxin shock may be due partly to the reduced inactivation of PGs through decreased PGDH activity in the lung and kidney.

Nakano J, McCloy RB, Prancan AV: *Circulatory and pulmonary airway responses to different mixtures of prostaglandins E and F in dogs. Eur J Pharmacol 24:61, 1973*

The circulatory and pulmonary airway resistance responses to intravenous administration of three different ratios (10:1, 1:1, 1:5) of PGE_2-$PGF_2\alpha$ were studied in anesthetized dogs. It was found that these mixtures of PGE_2-$PGF_2\alpha$ cause a dose-related decrease in systemic arterial pressure and a dose-related increase in pulmonary arterial pressure and airway pressure. It was concluded that there is evidence of marked differences in tissue specificity even when these different porstaglandins were given simultaneously, indicating that a preferential synthesis of PGE_2 or $PGF_2\alpha$ is not essential for the pathogenesis of clinical disorders with inflammatory reactions and bronchospasm, respectively.

Prancan AV, Hornbrook KR, Nakano J: *Effect of methylprednisolone on survival and on metabolic responses to e. coli endotoxin. Fed Proc 33:298, 1974*

Corticosteroid therapy in endotoxin shock is considered controversial. The survival of 349 male albino mice was recorded for 48 hr. following an i.p. injection of 10, 30 or 150 mg/kg of endotoxin alone or with methylprednisolone (6, 30 or 150 mg/kg, s.c.) given one hour before, simultaneously with, or one, two, four, or six hours after endotoxin (10 mg/kg, i.p.). In 194 other mice, glucose, glycogen, ATP, phosphocreatine (PC), lactate and pyruvate were measured in heart, liver and plasma after 10 mg/kg of endotoxin alone, or with 30 mg/kg of methylprednisolone one hour before, simultaneously with, or one, two or four hours after endotoxin. Samples were taken up to 12 hours after endotoxin injection. The 10 mg/kg dose of endotoxin produced an intermediate lethality in mice (LD_{60}). Methylprednisolone (30 mg/kg) increased survival significantly when given one hour before and up to 4 hours after endotoxin. Endotoxin depressed blood glucose, tissue glycogen, tissue ATP and PC below control level throughout the 12-hour period studied. Methylprednisolone, when given before or after endotoxin elevated blood glucose, tissue glycogen and tissue ATP and PC levels significantly above those of the endotoxin alone group. Corticosteroids enhanced survival of mice in endotoxin shock, perhaps by facilitating carbohydrate and high energy compound metabolism.

Perinatal Biology

Fadel HE, Misenhimer R: *Incarceration of the retroverted gravid uterus with sacculation. Obstet Gyncol 43:46, 1974*

A rare case of sacculation of the uterus secondary to incarceration of a retroverted gravid uterus is described. The inclusion of such a condition in the differential diagnosis of pelvic masses during pregnancy has been stressed. A review of similar cases is presented, and the management is discussed.

Fadel HE, Soliman MDE, Mehairy MMEl: *Serum complement activity in preeclamptic pregnancies. Int J Gyn Obstet 12:6, 1974*

Serum complement level was measured in 22 preeclamptic patients (11 mild and 11 severe). It was not different from the serum complement level in the 3rd trimester of normal pregnancy. This does not support a suggested immunologic etiology for preeclampsia. The evidence for this theory has been presented.

Pediatrics

Elders MJ, Garland JT, Daughaday WA, Fisher DA, Whitney JE, Hughes ER: *Laron's dwarfism: studies on the nature of the defect. J Pediatr 83:253, 1973*

Laron's syndrome is characterized by severe dwarfism, high circulating levels of immunoreactive growth hormone, and a failure to generate somatomedin in response to administration of human growth hormone. Studies conducted in a 7½-year-old boy with the syndrome indicate that the hypothalamic-pituitary mechanisms controlling growth hormone secretion are intact. However, those controlling the suppression of growth hormone release seem to be inoperative. The administration of exogenous human growth hormone failed to produce an acute metabolic response measured by mineral retention, nitrogen retention, somatomedin generation, or release of free fatty acid from adipose tissue; however, an unsustained growth response to long-term administration of human growth hormone was observed. The circulating growth hormone resembled normal human growth hormone immunologically and has the usual prolactin-like activity. These data suggest that the primary defect is tissue unresponsiveness to normal human growth hormone. An abnormality in the structure of growth hormone which is not essential for prolactin activity and immunoreactivity and a slow rate of growth hormone degradation in these patients cannot be excluded by available data.

Physiology

Benjamin B, Alaupovic P, Wang CS, Prancan A, Hinshaw LB: *Relationship of chemical structure to pathophysiologic properties of endotoxin from* serratia marcescens. *Circ Shock 1:61, 1974*

Prior investigations in a variety of animal species have demonstrated clearly that endo-

toxin administration is capable of eliciting a notable series of pathophysiologic events culminating in irreversible shock and death. Results from our previous studies have implicated the lipopolysaccharide portion of the endotoxin moiety as the responsible agent for these events. The present work was carried out to define more precisely the chemical nature of the active site of the endotoxin. Endotoxin from *Serratia marcescens* has been degraded by aqueous phenol or acetic acid hydrolysis into a number of chemically defined structural fragments. Intravenous injections of these fragments into unanesthetized or anesthetized animals was carried out to compare their biochemical, hemodynamic, and lethality relationships. Results suggest strongly that the typical pathophysiologic manifestations of endotoxin shock depend on the presence of ester-linked fatty acids in the lipid moiety of the endotoxin complex.

Maibenco HC, Krehbiel RH: *Reproductive decline in aged female rats. J Reprod Fert 32:121, 1973*

In a limited number of aged rats it was observed that, when implantation did occur, the average number of decidual reactions per uterine horn was comparable to that in younger females of the species and that the number of resorption sites was not above average.

The ability of the uterus of aged spayed animals receiving replacement hormones to produce a decidual reaction in response to stimuli is minimal. There was a higher incidence of leucocytic infiltration and infection in the reproductive tracts of aged animals. Such an unfavorable tubal or uterine environment was undoubtedly a contributing factor in the failure of ova to survive.

Plastic and Reconstructive Surgery

Curtin JW: *Reconstructive surgical procedures in myelodysplasia. South Med J 67:406, 1974*

The description of reconstructive surgical procedure in myelodysplasia focuses on surgical management of skin closure following removal of the myelomeningocele. Skin closure procedure consists of the construction of large, wide-based, double rotation flaps of skin and subcutaneous fat on both sides of the opening which are undermined widely to permit tension-free closing of the wound in a large "S" shape. If the wound is very large, split-thickness skin grafts can be used. Collaboration of various health service personnel is necessary to avoid such complications as pressure sores and ulcers, or to ensure their successful treatment. To achieve effective surgical management of pressure sores, a frequent complication in all instances of paraplegia, one must consider the patient's nutritional state, and possible anemia, control of spasms, and prevention of additional pressure sores. Surgical procedures for sacral, trochanteric, and ischial ulcers are outlined. Complications include necrosis of skin flaps, hematomas, infection, and wound separation.

Sadowsky C, Aduss H, Pruzansky S: *The soft tissue profile in unilateral clefts. Angle Orthod 43:233, 1973*

Changes in the soft tissue facial profile of seventy-five patients with complete unilateral cleft lip and palate, from four to eighteen years of age, were analyzed from serial lateral

cephalometric radiographs. The findings were compared with available data on matched noncleft control populations.

It was demonstrated that although there were differences between the cleft and noncleft groups, the children with clefts grew very much like noncleft children; further, that the surgical procedures employed in these studies did not result in midface deficiency. More specifically, the following results were reported:

1. The soft tissue profile (excluding the nose) of the cleft sample was less convex than the noncleft group and demonstrated slight flattening with increased age, whereas the soft tissue profile of the noncleft group did not change in time.
2. The soft tissue profile of the cleft sample changed much less than the underlying skeletal profile. The anterior surface of the bony maxilla became less convex with age due, in large measure, to the eruption of malposed incisors. The thickness of the soft tissue overlying the subnasal area, however, maintained a relatively constant position relative to the root of the nose.
3. Initially, the thickness of the soft tissue of the upper lip was thinner in the cleft sample but, in time, approximated the dimensions of the noncleft control.
4. The length of the upper and lower lip was greater in the cleft patients, while the rate of increase in length did not differ between the cleft and noncleft groups.
5. Although the length of the nasal bones was greater at all ages in the cleft sample, the nose was not as prominent and demonstrated less horizontal, but similar vertical growth, when compared with the noncleft control.
6. The length of the dorsum of the nose and the height of the nose was greater in the cleft than in the noncleft group. This may be due to a "tension effect" on the tip of the nose resulting from lip repair and the inherently short columella.
7. The configuration of the nasal outline in terms of both hard and soft tissue suggests that the nose is positioned relatively backward and downward in the cleft sample.
8. The greatest effect of nasal growth on the profile was observed after twelve years of age, particularly between twelve and fifteen years. This is the same pattern of growth as has been reported for noncleft populations.

Psychology and Social Sciences

Garron DC, Narin F, Bruyn GW, Klawans HL Jr: *The effect of L-dopa on intellectual functioning in idiopathic parkinsonism.* In: *Parkinson's disease, rigidity, akinesia, behavior, Vol 2: Selected communications on topic, Edited by J. Siegfried. 1973, Bern, Hans Huber*

L-dopa, which improves motor functioning in parkinsonism, is reported to improve intellectual functioning also. Difficulties in evaluating this purported intellectual improvement are a) etiologic diversity and irreversible dementia in some patients, b) absence of control subjects, and c) selection of appropriate intellectual tests. Comparison of eight akinetic and ten non-akinetic patients with idiopathic parkinsonism, and eleven control subjects individually matched for age, race, sex and education, on alternate forms of four aspects of intelligence (vocabulary, word transformation, attention, and verbal conceptualization), before L-dopa treatment and again after eight weeks of treatment, indicates that L-dopa increases the speed of response of akinetic patients, improves the performance of akinetic patients only on a test of verbal conceptualization, and improves the performance of non-akinetic patients only on a test of attention. These results cannot be taken as strong evidence for an improvement in intellectual functioning as a result of L-dopa in patients with parkinsonism, but do suggest that the appropriate group for a definitive study would be non-demented but moderately impaired patients with the akinetic form of idiopathic parkinsonism, and the appropriate tests would be of conceptual problems unaffected by motor efficiency.

Surgery

John DR, Straus A: *A technic for neonatal thymectomy in marmoset monkeys. Lab Anim Sci 24:343, 1974*

A technic was developed for thymectomy of neonatal marmosets under diethyl ether anesthesia. Thymectomy was performed within 24 hours of birth. Oral antibiotic therapy was continued 7 days postoperatively. Preliminary experiments indicated that the degree of impairment of cell-mediated immunity is not as great in neonatally thymectomized marmosets as in mice.

Merkel FK, Ing TS, Ahmadian Y, Lewy P, Ambruster K, Oyama J, Sulieman JS, Balman AB, King LR: *Transplantation in and of the young. J Urol 3:679, 1974*

Useful techniques for renal transplantation in pediatric recipients have been described for all age groups. *En bloc* removal and perfusion of donor cadaver kidneys are advocated. The use of iliac conduits in conjunction with renal transplants is described. Pediatric recipients six to ten years old achieve greater success than recipients less than six years old.

Techniques for implantation of pediatric donor kidneys into recipients of all ages are described. *En bloc* transplantation of both donor kidneys is preferred when the donor kidneys are very small and the recipient is an adult. Patients receiving cadaver kidneys from donors six to ten years old enjoy the same success as those with young adult donors. Recipients of kidneys from donors less than six years old achieve less success.

Urology

Mobley JE: Congenital torsion of the penis. *J Urol 109:517, 1973*

Eighty-seven patients with congenital torsion of the penis have been reported in the medical literature since its first description in 1857. This malformation is much more commonly seen, however, as any pediatrician or urologist with extensive clinical experience will confirm.

Penile torsion can be defined as a congenital malformation of unknown cause, in which there is rotation of penis on its longitudinal axis. Eighty percent of the time this rotation is to the patient's left. The extent of rotation is usually 90 degrees or less, although one patient with 270 degrees of rotation has been described. Simple penile rotation is usually of no clinical significance. Only when there is associated chordee, hypospadias or other abnormality is surgical therapy required. The presence of torsion associated with chordee or hypospadias adds one surgical step to treatment. A circumferential incision is made at the site of torsion, incising skin and dartos tunic. By placing sutures carefully the rotation is corrected. Six months should elapse before necessary additional surgical procedures are undertaken.

Mobley JE, Hardison W: *Nephrolithiasis following intestinal bypass for obesity. Urology 3:639, 1974*

A case of nephrolithiasis following intestinal bypass for obesity is presented. The pathophysiology of stone formation in such patients is discussed. Cholestyramine therapy is recommended for those patients with hyperoxaluria.

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